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- ***ORIGINAL RESEARCH -***

All Consecutive Ab Externo SIBS Microshunt Implantations with Mitomycin C: 1-year outcomes and risk factors for failure

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Short Title:
Subconjunctival Microshunt 1-year Outcomes and Risk-Factors

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Abstract

Subconjunctival Microshunt 1-year Outcomes and Risk-Factors

Purpose: Present effectiveness, risk factors for surgical failure, and adverse events over 12-months in a consecutive diverse cohort of glaucoma patients that underwent solo or combined *ab externo* SIBS microshunt with mitomycin C (MMC) with or without previous subconjunctival surgery.

Study design: Retrospective, consecutive, interventional case series.

Methods: Consecutive glaucomatous eyes on maximally tolerated medical therapy received *ab externo* SIBS microshunt with MMC implantation as a solo or combined procedure with phacoemulsification from July 2015 to January 2020. The primary outcome was the proportion of eyes at 12-months with (1) no two consecutive IOPs >17mmHg or clinical hypotony, without (complete success) or with (qualified success) glaucoma medications; and (2) ≥20% reduction from baseline IOP. Secondary outcomes included upper IOP thresholds of 14 and 21mmHg with and without a 20% IOP reduction from baseline, median IOP, medications, risk factors for failure, post-operative interventions, complications, and reoperations.

Results: A total of 436 eyes underwent surgery; 86 (20%) combined with phacoemulsification, 127 (29%) in eyes with refractory glaucoma, and 234 (51%) stand-alone procedures in non-refractory eyes. Complete success (6 to 17mmHg with no medications) was achieved in 64.0% of combined eyes, 58.1% of refractory eyes, and 74.8% of stand-alone non-refractory eyes; and qualified success rates (6 to 17mmHg with medications) were 90.7%, 84.7%, and 92.4% of eyes, respectively. At 12-months, 67% of eyes were medication free. Significant risk factors for failure included combined procedures in refractory eyes (HR 3.2; 95%CI 1.4 – 7.4), receiving <0.4mg/mL of MMC (HR 2.2; 95%CI 1.6 – 3.1), refractory eyes (HR 1.7; 95%CI 1.2 – 2.5), combined procedures (HR 1.6; 95%CI 1.0 – 2.5), and each additional baseline medication class (HR 1.3; 95%CI 1.1 – 1.5). Post-operative complications occurred in 31% of eyes, and more often in those receiving ≥0.4mg/ml MMC (OR 2.2, 95% CI 1.2 – 3.8). Needling occurred in 12% of eyes, with significantly higher frequency in refractory eyes (23%) and combined procedures (13%) compared to stand-alone (7%; p<0.001). Revisions and reoperations occurred in 4% and 1.4% of eyes, respectively.

Conclusions: One-year follow-up data from this large and diverse cohort support promising rates of qualified and complete surgical success with decreased medication burden and few post-operative complications and interventions. Combined phacoemulsification, refractory glaucoma, and receiving <0.4mg/ml MMC significantly reduced surgical success rates.

Keywords: glaucoma surgery, subconjunctival filtering, microshunt, SIBS, refractory, combined

Introduction

While initially treated most often with topical glaucoma medications and/or laser trabeculoplasty, 8.5% of glaucoma patients undergo treatment escalation to a surgical intervention over a given 5-year period.[1] A doubling in the number of glaucoma patients is predicted to occur worldwide by 2040,[2] with the need for surgical treatment increasing in parallel.[3,4] The introduction of many new glaucoma surgical procedures in recent years underscores the need for greater clarity regarding the risks and expected clinical course associated with a chosen glaucoma procedure and how patient factors and the exact treatment approach influence outcomes.

The advent of microinvasive glaucoma surgery has led to potentially safer surgical approaches to lowering intraocular pressure (IOP) and decreasing drop burden.[5] Classic internal microinvasive glaucoma surgery targeting the trabecular meshwork outflow system can address trabecular meshwork dysfunction but can be limited by impaired collector system drainage and ultimately episcleral venous pressure. Subconjunctival procedures such as trabeculectomy and tube shunts have long been the mainstay of glaucoma surgical treatment; these approaches bypass the area of resistance within the conventional outflow system by shunting the aqueous humor to the sub-Tenon and subconjunctival space. However, a significant limiting factor of the subconjunctival outflow pathway is its unpredictability. In response, subconjunctival microshunt devices with a controlled lumen size and length were designed to regulate flow and mitigate the risk of hypotony. Early studies suggest that this may be a viable alternative to reliably achieving low IOP targets,[6,7] however, studies reporting long-term data from large patient populations undergoing novel glaucoma surgical procedures remain elusive in the published literature.

The Preserflo Microshunt (SIBS Microshunt, Santen) is comprised of the same inert poly(styrene-block-isobutylene-block-styrene), or "SIBS" material as coronary artery stents – acting to limit scarring and chronic inflammatory reactions.[8] This microshunt has the potential to create a posterior bleb and outflow pathway, avoiding the higher risk associated with limbal blebs sometimes seen after trabeculectomy or deep sclerectomy. The length and internal lumen diameter of the SIBS microshunt restrict outflow by leveraging the Hagen-Poiseuille equation and the radial fins positioned within the scleral insertion site function to mitigate peritubular flow - all contributing to the goal of avoiding hypotony.

We know that patient factors can have a significant impact on surgical success. For instance, previous subconjunctival filtering surgery is a well-known risk factor for failure.[9,10] Likely, the same factors which caused the original surgery to fail, combined with new scarring at the surgical site, drive surgical failure.[11] Different interventions may be impacted differentially by previous failed interventions; for instance, in the TVT study, tube shunts were more robust than trabeculectomy in refractory patients.[12] Further, there has also been significant debate in the literature on the impact of combining subconjunctival filtering surgery with cataract surgery. Many studies of subconjunctival filtering surgery show decreased success rates, more complications, and/or more interventions when these surgeries are combined with cataract surgery.[13–20] The SIBS microshunt shares some features of both trabeculectomy and a tube shunt, so its success in refractory patients or in combination with phacoemulsification relative to eyes without previous subconjunctival surgery or stand-alone procedures is unknown. Many previous studies are marred by low sample sizes, confounding by indication, short follow-up duration, and differential loss to follow-up. These important inherent clinical considerations cannot be randomized in a prospective fashion, so the best investigational approach is to measure outcomes relative to other populations and account for confounders as best as

possible. This large inclusive study population allows investigation of all patients that received the novel SIBS microshunt within our center and systematically investigates surgical success, interventions, complications, and reoperations in the context of patient demographic and clinical characteristics.

Methods

This study reports 1-year outcomes, from an investigator-initiated, single-center, retrospective interventional case series of consecutive eyes receiving microinvasive bleb surgery (MIBS) with a SIBS microshunt and MMC between July 1, 2015, and January 1, 2020. A single surgeon and clinical fellows, under direct supervision, working in an academic ophthalmology centre in the Greater Toronto Area, Canada, performed each surgery. Institutional review board approval was received from Trillium Health Partners for this study, which adhered to the tenets of the Declaration of Helsinki. Every patient gave informed consent for surgery. Baseline preoperative characteristics recorded include demographics (age, eye, sex, ethnicity, diabetes status) and ocular characteristics (best-corrected visual acuity [BCVA]; IOP at which the decision for surgery was made [decision IOP]; glaucoma medication classes (in which carbonic anhydrase inhibitors were included); glaucoma diagnosis; cup-to-disc ratio; visual field mean deviation; and history of previous cataract surgery, other ocular surgery, or laser trabeculoplasty).

Inclusion and Exclusion Criteria: Data on consecutive eyes were collected. The microshunt was implanted in eyes exhibiting visual field progression while on maximally tolerated medical therapy and/or with an IOP above target. Stand alone procedures, procedures combined with phacoemulsification and those in eyes with prior surgical intervention were included in the analysis. Eyes were excluded if they had less than 1 month of follow-up.

Microinvasive Bleb-forming Surgery with Microshunt Implantation: The procedure for MicroShunt implantation has been previously described in detail.[21] In summary, a two-clock-hour fornix-based conjunctival peritomy was carried out after careful inspection of the conjunctiva to plan the placement of the device. Care was taken to avoid areas of conjunctival scarring or antimetabolite toxicity (thin conjunctiva, large ropy vessels and tissue that is difficult to mobilize). The superonasal quadrant was utilized (n=363), followed by superotemporal (n=35), inferonasal (n=44) or inferotemporal (n=17) if no other viable region of conjunctival tissue was available. Careful dissection of the Tenon layer was carried out to liberate all connections to the underlying episclera and produced a large space between the rectus muscles. The area posteriorly between the muscle bellies and anteriorly under Tenon's capsule were then treated with three LASIK Merocel sponges (BVI, Waltham, MA, USA) soaked in MMC for a total of two minutes, taking care to prevent any contact with the limbus. Initially, it was determined that blebs were posterior and diffuse with increased vascularity, resulting in a rise in MMC concentration over the course of the trial to increase the likelihood of surgical success. MMC doses of 0.2 mg/mL were employed for the first patients, and then 0.4 mg/mL and 0.5 mg/mL for the following patients. After making a 3-mm mark posterior to the limbus, a 1-mm slit-angled microknife was used to cut a 1-mm-wide scleral tunnel through the AC at the trabecular meshwork. The SIBS microshunt was inserted into the scleral tunnel with its bevel pointing up

using curved tying forceps, and its fins were pushed into the scleral pocket. Flow through the distal end of the microshunt was validated by injecting BSS in the AC and pressurizing the eye and visualizing the simultaneous egress of fluid from the distal end of the microshunt. A 9-0 vicryl suture was then used to seal the conjunctiva and tenons in separate layers, making sure the implant was not stuck in the tenon layer.

Post-operative Management: After the surgery, patients were told to cease all glaucoma medications and begin taking steroid drops every two hours for the first week, followed by a slow taper over 6 to 10 weeks according to the surgeon's discretion based on IOP and bleb morphology. Patients were examined on the first post-operative day, the third post-operative day, and then as often as the surgeon deemed necessary. All visits included a full biomicroscopy exam and bleb examination. A Seidel test was performed routinely during the first 2 weeks postoperatively. A dilated fundus exam was performed during the first post-operative week and repeated as needed if there were any signs of clinical hypotony. Reoperations, needling, digital ocular compression, AC reformation, reintroduction of glaucoma medicines, and surgical adjustments were carried out at the surgeon's discretion. A 25-gauge trocar was used for needling procedures at the slit lamp. Prior to beginning the needling, 0.1 mL of MMC (0.4 or 0.5 mg/mL) was administered using a 30-gauge needle and a long subconjunctival track. After waiting for 20 minutes, the trocar was again advanced through the subconjunctival track and used to break up as much of the fibrotic capsule as needed or free the implant from adhesions. At the end of the procedure, at the surgeon's discretion, viscoelastic was also injected subconjunctivally. After the procedure, topical antibiotics were used for 1 week and steroid drops every 2 hours for the first week, followed by a slow taper over 6-10 weeks.

Surgical Revision: The conjunctiva was meticulously dissected during revisions, and the surrounding scar tissue was removed. MMC (0.5 mg/mL) soaked sponges were applied for two to three minutes intraoperatively with the additional use of a posterior intra-tissue MMC injection prior to surgery at surgeon discretion. Next, pressurization of the anterior chamber with BSS and monitoring for flow from the distal end of the microshunt was performed to assess device patency. The device was flushed with a 23-gauge thin-walled cannula. If any abnormalities in the device were discovered, such as poor flow or intraluminal obstruction, it was replaced with a new implant.

Primary Outcome: The proportion of eyes maintaining surgical success at one year was the primary outcome. Complete success was defined by the following criteria: 1) no two consecutive IOP readings greater than 17 mmHg; 2) no clinical hypotony (defined as: IOP less than 6 mmHg and more than 2 lines of vision loss from sequelae of hypotony); 3) maintain ≥20% IOP reduction from the time the decision was made to undergo surgical intervention (decision IOP); and 4) no use of glaucoma medications. Qualified success permitted the use of glaucoma medications. Loss of light perception or surgical reoperations for glaucoma were defined as immediate failures. Within the first post-operative month, IOP outside threshold and glaucoma medication use were not regarded as failures. Instances of in-clinic post-operative interventions, such as needling, were not regarded as failures at any point during follow-up.

Secondary Outcomes: Secondary efficacy outcome measures used modified upper IOP thresholds of 14 mm Hg and 21 mm Hg for complete and qualified success criteria with and without a 20% IOP reduction from baseline. Time to first medication use, median IOP, medication burden, and BCVA in logarithm of the minimum angle of resolution (logMAR) at the most recent follow-up or at reoperation are also recorded. We also investigated potential risk

factors for failure, including sex, age, ethnicity, right vs. left eye, lens status, history of trabeculoplasty, glaucoma type, glaucoma severity, decision IOP, preoperative vision, diabetes status, and MMC dose.

Safety Outcomes: Minor complications (including leak or dehiscence, hyphema, vitreous haemorrhage, choroidal detachments, macular folds, prolonged inflammation, corneal decompensation, macular edema, diplopia, iris incarceration, or blocked or exposed microshunt), serious complications (including angle closure, retinal detachment, suprachoroidal haemorrhage, malignant glaucoma, blebitis, enophthalmitis, or no light perception vision), interventions during the post-operative period, and reoperations for glaucoma were recorded and analysed for potential risk factors.

Statistical analysis: SAS university edition software was used to conduct all statistical analyses (SAS Institute Inc, Cary, North Carolina, USA). Graphs were created using Prism 9 or SAS university edition software (Version 9.1.2, GraphPad Software, LLC). Categorical variables were represented as proportions, and Fisher exact tests were used for inter-group comparisons. Continuous outcomes were described as means (standard deviation) or medians (interquartile range [IQR]), depending on the distribution of the data, and then compared using Wilcoxon tests or 2-sided t-tests, as indicated by normality. LogMAR conversions were made for all Snellen visual acuity measures. To statistically account for loss to follow-up, overall treatment success was evaluated using survival analysis and visualized with Kaplan-Meier curves. Using Kaplan-Meier curves for the various IOP cut-offs for complete and qualifying success, the findings were stratified according to the risk factors for failure described below, and the log-rank test was performed to assess differences across strata.

Identification of risk factors for surgical failure and other adverse events was accomplished using a Cox proportional hazard model. The following variables were examined on a univariable (crude) and multivariable (adjusted) basis: age, sex, eye, phakic status, disease severity, ethnicity, elevated decision IOP, MMC dose, and diabetes diagnosis. To approximate data with equivalent failure intervals, the Efron method was used. No competing risk factors were believed to have the potential to affect data censoring. Regression analysis with a condition index cutoff of >30 was used to estimate collinearity. To ascertain if the conditions for proportional hazards were satisfied for each variable, Martingale residuals were utilized. If this presumption was violated, it was addressed by stratifying the model according to the nonproportional variable or by including a time-variable interaction term. The time-variable interaction term was excluded from the final model if the regression coefficient indicates that it only contributes 1% or less to the change in hazard over time. On both a univariate and multivariate basis, secondary categorical or continuous outcomes were examined using a general linear model on both a univariate and multivariate basis. As some patients had both eyes enrolled, we accounted for this intracluster dependence using a frailty model with an approach popularised by Lee, Wei, and Amato (1992),[22] which estimates the regression parameters in the Cox model by maximum partial likelihood estimates under an independent working assumption and employs a robust sandwich covariance matrix estimate. Statistical significance was defined as a 2-sided P value less than 0.05.

Results

Study population and baseline characteristics: This study identified 459 eyes from 391 patients who underwent SIBS microshunt implantation with MMC between July 1, 2015, and January 1, 2020. Twenty-three eyes had less than 1-month follow up and were excluded from the analysis. Table 1 summarizes the baseline characteristics of all included eyes. Visual field mean deviation and cup-to-disk ratio were not normally distributed in our study and thus reported as median (IQR) in Table 1, however, to facilitate reference to other published literature, the study population mean (±standard deviation) cup-to-disk ratio was 0.81 (±0.19) and mean (±standard deviation) visual field MD was -12.48 (±10.0) dB. Eyes undergoing combined procedures were older (29% >70 years), had worse visual acuity (49% ≥0.4 logMAR), and a higher rate of previous laser trabeculoplasty (69%). Refractory eyes had worse visual acuity (41%≥0.4 logMAR), visual field mean deviation (median [IQR] MD -14.3 [-22.3 to -5.6]), and disease severity (67% advanced).

The final cohort included 436 eyes from 376 patients with an 86% follow-up rate over 1-year. The follow-up rate for stand-alone non-refractory eyes was 88%, for eyes with combined procedures it was 84%, and for eyes with refractory glaucoma it was 83%.The median (IQR) follow-up time was 14.1 (12.9 - 16.6) months for the entire cohort, 14.0 (12.6 - 16.6) months for combined procedure eyes, and 13.9 (13.0 - 16.1) months for refractory eyes (p=0.34).

Primary Outcome: Surgical Success at 1-year (Figure 1) defined as no IOP above 17 mmHg or below 6 mmHg (also with clinical hypotony) on 2 consecutive visits and a 20% reduction from the decision IOP. Complete success occurred in 74.8% of stand alone non-refractory eyes, 64.0% of combined procedure eyes, and 58.1% of refractory eyes. Qualified success occurred in 92.4% of stand alone non-refractory eyes, 90.7% of combined procedure eyes, and 84.7% of refractory eyes. Median (IQR) time to failure was 5.2 (1.9 – 7.4) months (n=60) for stand alone non-refractory, 5.5 (1.9 - 9.3) months (n=31) for combined procedures, and 4.6 (2.3 - 6.9) months (n=52) for refractory eyes. Two failures occurred due to clinical hypotony in the stand alone non-refractory group, and one in the refractory group.

Secondary IOP Outcomes: Using an upper IOP cut-off of 14 mmHg, complete success was achieved in 71.0% of stand alone non-refractory eyes, 61.6% of combined procedure eyes, and 53.2% in refractory eyes. Qualified success was achieved in 92.0% of stand alone non-refractory eyes, 87.2% in combined procedure eyes, and 83.1% in refractory eyes. With an upper cut-off of 21 mmHg, complete success was achieved in 75.2% of stand alone non-refractory eyes, 66.3% of combined procedure eyes, and 58.9% for refractory eyes. Qualified success was achieved in 93.7% of stand alone non-refractory eyes, 91.9% of combined procedure eyes, and 84.7% in refractory eyes.

Sensitivity Analysis for Primary Outcome: Surgical success at 1-year (Figure S2) defined using IOP cut-offs of ≥ 6 mmHg (also with clinical hypotony) and ≤ 14, 17 and 21 mmHg, without the requirement for a 20% reduction in IOP from baseline, was achieved without medication use in 81.5%, 87.0%, and 89.1% percent of stand alone non-refractory eyes, respectively. Qualified success was achieved in 92.9%, 94.1%, and 95.4% of eyes. In eyes that underwent combined procedures, complete success was achieved in 72.1%, 77.9%, and 82.6% of eyes, and qualified success in 89.5%, 91.9%, and 94.2% of eyes. In refractory eyes, complete success was achieved in 62.1%, 70.2%, and 75.8% of eyes, and qualified success in 83.9%, 87.1%, and 90.3% of eyes.

Characteristics Associated with Surgical Failure: For the Cox regression analysis identifying risk factors for failure (Figure 2), we used the 6-14 mmHg IOP cut-off with ≥20% IOPR – as it was the strictest of the criteria, providing the highest event rate and therefore statistical power. Procedures in refractory eyes combined with phacoemulsification (hazard ratio [HR] 2.00; 95% confidence interval [CI] 0.93 – 4.33), eyes receiving an intraoperative MMC dose < 0.4mg/ml (HR 1.90; 95%CI 1.40 – 2.59), stand-alone procedures in refractory eyes (HR 1.62; 95%CI 1.17 – 2.26), and each additional medication class at baseline (HR 1.22; 95%CI 1.06 – 1.41) were associated with an increased risk of failure on a univariable basis. In the adjusted analysis, procedures in refractory eyes combined with phacoemulsification (HR 3.22; 95%CI 1.41 – 7.36), eyes receiving a MMC dose of < 0.4 mg/mL (HR 2.21; 95%CI 1.59 – 3.06), stand-alone procedures in refractory eyes (HR 1.73; 95%CI 1.20 – 2.49), combined procedures in non-refractory eyes (HR 1.61; 95%CI 1.02 – 2.54), and each additional medication class at baseline (HR 1.26; 95%CI 1.08 – 1.46) was associated with a higher risk of failure on a multivariate basis. Decision IOP, POAG, ethnicity, left eye, female sex, poor preoperative vision, hypertension, diabetes, age <70 years, previous trabeculoplasty, previous tube shunt, mean deviation less than -12 dB on visual field testing, and pseudophakia all had hazard ratios over one but these associations with surgical failure did not attain statistical significance. No variables were impacted by collinearity or non-proportionality, as none exceeded the maximum Condition Index threshold and martingale residuals were symmetrically distributed. The clustering effect of some patients having two eyes enrolled in the trial had no significant impact on the study outcomes; Figure 2 illustrates that the adjusted multivariate model's conclusions are not substantially different from the fragility model.

Intraocular pressure, medication use and best-corrected visual acuity: At baseline, the median IOP was 20 (17 - 27) mmHg and the median medication use was 4 (3 - 4) for stand alone non-refractory; 23 (20 - 29) mmHg and 4 (3 - 4) for combined procedures; 21 (18 - 28) mmHg and 4 (3 - 4) for refractory eyes, respectively. At 1-year, the median IOP was 12 (10 - 15) mmHg and the median medication use was 0 (0 - 0) for stand alone non-refractory; 14 (11 - 19) mmHg and 0 (0 - 1) for combined procedures; and 14 (10 - 17) mmHg and 0 (0 - 2) for refractory eyes, respectively (Figure 3). Eyes that received ≥0.4mg/ml MMC intraoperatively had significantly lower median IOP and medication requirements (Figure 3B) at 9-months (IOP p=0.03; meds p=0.01) post-operatively and at the 12-month follow-up (IOP p<0.0001; meds p<0.0001). There was no significant difference in median IOP or medication requirements at any time post-operatively in eyes that underwent combined surgery (Figure 3C) compared to stand-alone procedures (p>0.05). Refractory eyes had a significantly increased medication burden at 9-months (p=0.001) and 12-months (p<0.0001) post-operatively compared to non-refractory eyes, however there was no significant difference found in median IOP at any follow-up visit (Figure 3D). An individualized representation of patient IOP changes, censoring for reoperations, from the decision for microshunt implantation to the first reported visit 1-year postoperatively is shown in Figure 4.

A patient-level representation of medication changes from baseline to 1-year follow-up is presented in Figure 5. At one year, 125 (73.9%) stand alone non-refractory eyes were glaucoma medication free, with 35 (61.4%) combined procedure eyes and 44 (54.2%) refractory eyes remaining glaucoma medication free. Of the stand alone non-refractory eyes that achieved qualified success, at 1-year 177 (88.1%) were on fewer medications than at the time the decision was made for surgery – 20 (10.0%) were on the same, and 4 (2%) were on more. Of the eyes combined with phacoemulsification that achieved qualified success, 58 (80.6%) were

on fewer medications, 12 (16.7%) were on the same, and 2 (3%) were on more. For refractory eyes, 86 (82.7%) were on fewer medication, 13 (12.5%) were on the same, and 5 (5%) were on more medications after 1-year follow-up.

Time to first post-operative medication use is presented in Figure S1 and occurred a median (IQR) of 6.9 (3.2 - 10.0) months after surgery for stand alone non-refractory eyes, 5.5 (3.3 - 9.6) months in eyes with combined procedures, and 6.9 (3.8 - 10.5) in refractory eyes. Refractory eyes (HR 1.36; 95%CI 1.12 - 1.64), those with POAG (HR 1.44; 95%CI 1.06 - 1.98) and eyes experiencing IOP > 10 mmHg within the first post-operative month (HR 1.58; 95%CI 1.16 - 2.14) were more likely to receive medications earlier in the post-operative period.

In refractory and non-refractory eyes that did not undergo combined phacoemulsification, the median BCVA went from 0.18 (0.1 - 0.4) logMAR at baseline to 0.18 (0.1 - 0.5) logMAR at 1-year ($p > 0.05$, n=346), with 209 (61.3%) eyes maintaining baseline vision or better. Fifty-six (15.5%) eyes lost more than 2 lines of vision at last follow-up or reoperation. None of the investigated baseline factors were found to be significantly associated with time to visual recovery.

Complications: One hundred thirty-four eyes (30.7%) had a total of 229 complications (Table 2), occurring with the highest frequency within the first post-operative month. Refractory eyes experienced the most complications (n=43, 34%). There was no significant difference in complication free survival time between refractory eyes, eyes undergoing combined procedures, and non-refractory stand-alone procedures (Figure 6A). In total, 10 eyes (2.2%) experienced persistent clinical hypotony with associated vision loss. Hypotony maculopathy was present in 17 eyes and occurred with significantly greater frequency in refractory eyes relative to both non-refractory eyes and eyes undergoing combined procedures (10% vs. 2% and 5%; $p<0.03$). Early choroidal detachments all resolved with conservative management (involving topical steroids and atropine 1%) except in 14 cases (3%) which underwent viscoelastic (Healon GV or Provisc) anterior chamber reformation. In these cases, IOP ranged from 1 to 6 mmHg before anterior chamber reformation. Immediately after the procedure IOP would measure in the high teens to low twenties and then normalize to the low teens over the following week. Two eyes (0.5%) received a second anterior chamber reformation and two eyes (0.5%) received three AC reformations to stabilize the AC. Four eyes (0.9%) received posterior sub-Tenon triamcinolone acetonide injection (40 mg/mL x 0.2 mL) for persistent late choroidal detachment. All choroidal detachments resolved before 6 months.

Five eyes (1.1%) experienced significant complications such as loss of light perception vision (n=1, 0.2%), malignant glaucoma (n=2, 0.5%), microshunt erosion (n=1, 0.2%), or endophthalmitis (n=1, 0.2%). The patient that became NLP post-operatively was a 77-year old diabetic that developed a fungal corneal ulcer on post-operative day 96, ultimately undergoing enucleation several months later secondary to fungal infection. Malignant glaucoma only occurred in patients undergoing procedures combined with phacoemulsification and with short axial length. In both cases of MG, maximally tolerated medical therapy and cycloplegic were reinitiated. This was adequate to resolve one case, however the other received an AC reformation and needle irido-zonulo-hyaloido-vitrectomy (IZHV) before resolution – thereafter neither case received ongoing glaucoma medications.

Eyes receiving an intraoperative dose of ≥0.4 mg/ml MMC were statistically more likely (36.8% vs. 20.8%) to experience post-operative complications (OR 2.2, 95% CI 1.2 – 3.8), with a

tendency for these excess complications to occur within the first post-operative month (23.7% vs. 10.6%). In total, eyes receiving 0.2mg/ml MMC (n=96) experienced complications at a rate of 22.8%, those receiving 0.4mg/ml (n=210) had a rate of 35.4%, and those receiving 0.5mg/ml (n=130) experienced a rate of 42.3% (chi-square p<0.01).

Post-operative Interventions: There was a total of 181 distinct interventions performed in 82 eyes (18.8%; Table 3). The most common intervention was needling (11.9%), followed by AC reformation (7.1%) and AC tap (2.9%). Eyes receiving less than 0.4 mg/ml MMC intra-operatively received post-operative interventions more frequently than eyes receiving 0.4 mg/ml or higher, but this difference did not reach statistical significance (22.9% vs. 17.7%; OR 1.4; 95% CI 0.8 – 1.3). Digital ocular compression was analyzed separately and was performed in 89 (20.4%) eyes overall, often for diagnostic purpose (to evaluate microshunt patency function), and potentially therapeutic (to flush the microshunt and improve bleb flow).

Characteristics Associated with Receiving Needling: Needling numbers were modest (n = 52 eyes; 11.9%), with two eyes receiving a second needling. Refractory eyes undergoing a combined procedure (HR: 8.98, 95% CI 3.05 – 26.45), combined procedures in non-refractory eyes (HR: 4.06; 95%CI 2.08 – 7.94), eyes receiving <0.4 mg/ml intra-operative MMC (HR: 3.18, 95% CI 1.95 – 5.18), and eyes with an IOP measured ≥ 10 mmHg during the first post-operative month (HR: 2.06, 95% CI 1.25 – 3.39) were all significantly associated with a higher rate of needling (Figure S2). The median (IQR) time to needling was 5.4 (1.1 – 11.9) months, respectively. Mean and median IOP were 23.5 mmHg and 21 mmHg, and eyes were on a mean of 0.9 classes.

Revisions and Reoperations: Eighteen eyes (4.1%) experienced a bleb revision at a median (IQR) of 7.6 (4 – 9) months post-operatively (Table 4). Of the seventeen eyes that underwent bleb revisions, seven (41.2%) continued with uneventful follow-up and ten (58.8%) subsequently received a microshunt exchange. One patient receiving an exchange after bleb revision due to increased IOP experienced a microshunt erosion during post-operative month 11, this POAG patient's microshunt was implanted in the supertemporal quadrant and they had no history of previous subconjunctival surgery; however, the patient had advanced glaucoma, was of African descent, and did receive three doses of MMC (0.5mg/ml) – with the combined surgery, needling, and bleb revision. Plans were made to implant a new shunt at a new clock hour, however this occurred after the study follow up period.

Reoperations, defined as undergoing another glaucoma procedure, occurred in six (1.4%) eyes at a mean (IQR) of 7.5 (6.6 – 9.9) months post-operatively (Table 4). Two (0.5%) eyes underwent Ahmed Glaucoma Valve (New World Medical, Inc., USA) implantation for elevated IOP at post-operative months 5.2 and 9.6 – both with IOPs > 25 mmHg and on 4 medication classes. One eye received a Baerveldt Glaucoma Implant (Johnson & Johnson Surgical Vision, Inc., USA) secondary to persistently elevated IOP (>25 mmHg) while on maximally tolerated medical therapy. Two (0.5%) eyes underwent cyclophotocoagulation after multiple failed needling attempts with IOPs of 30 and 40 mmHg on 4 medication classes. One eye underwent enucleation 8.4 months post-operatively; this eye had known herpetic corneal colonization prior to surgery and developed a herpetic corneal ulcer with superimposed fungal infection three months after surgery. This led to endophthalmitis and the ultimate enucleation.

Receiving < 0.4mg/ml intra-operative MMC was not significantly associated with an increased risk of undergoing revision (OR 1.0; 95%CI 0.4 – 2.8) or reoperation (OR 3.6; 95%CI 0.8 – 15.1)

for glaucoma, though the sample size and event rate are too low to make any definitive conclusions.

Discussion

This study reports on the largest and most diverse cohort of SIBS microshunt patients reported to date. It represents a potentially externally generalizable set of patients, including a broad range of ethnicities, both stand-alone implantations and combined with cataract surgery, as well as varying glaucoma disease level status, surgical history, and levels of intraoperative MMC. The efficacy results were reassuring: 58.1% of eyes with refractory glaucoma achieved complete success (17mmHg upper threshold), 64.0% of eyes combined with phacoemulsification, and 74.8% of stand-alone eyes. Qualified success, with the same IOP thresholds but allowing for medication use, was achieved in 81.9%, 86.1%, and 86.8% of eyes, respectively. Needling was the most common post-operative intervention (12%) and was more common among combined surgeries, MMC dose of 0.2mg/ml, and when the IOP was >10mmg in the first month post-operatively. Overall, 4.1% received a revision, and 1.4% received a reoperation. Most complications occurred in the early post-operative period, and the rate was higher in eyes with MMC doses of >0.2mg/cc. Ten (2.2%) eyes experienced persistent clinical hypotony associated with vision loss.

The outcome differences in the three surgical groups, stand-alone, refractory, and combined with phacoemulsification, represent important clinical findings. As expected, the refractory eyes, all of which had received previous sub-conjunctival surgery, had lower success rates than the other cohorts (crude HR of failure 1.62; 95%CI 1.17 – 2.26, and adjusted HR 1.73; 95%CI 1.20 – 2.49). Because it is impossible to randomize this type of analysis, there is potential for confounding. Refractory eyes in this study had worse vision than the stand-alone group (though not the combined group), more advanced disease, and were more likely to have had previous cataract surgery than the stand-alone group. However, the crude and adjusted HRs were similar, and none of the listed factors above were independently associated with failure. Nevertheless, unmeasured confounders could have influenced the results. Unmeasured risk factors for failure found among the refractory eyes could have overestimated the impact of previous sub-conjunctival surgery on failure, and unmeasured risk factors for failure found among the stand-alone and combined eyes may have underestimated the impact of previous sub-conjunctival surgery on failure. It stands to reason that, in addition to scarring from the first surgery, the same factors that predisposed the initial surgery to fail would adversely influence the efficacy of the second surgery.

Combined surgery also appeared to be a risk factor for failure relative to stand-alone surgery. Again, there will likely never be a randomized control trial to assess the difference in combined versus stand-alone surgery to balance confounders. On a crude basis, there did not seem to be a strong effect; however, after adjusting for confounders, combined surgery was significantly associated with failure (HR 1.61; 95%CI 1.02 – 2.54) as well as a dramatically higher frequency of needling (HR: 3.4, 95% CI 1.8 – 6.5) which also points towards decreased efficacy.

There has been significant debate in the literature on the impact of combining subconjunctival filtering surgery with cataract surgery. Many studies of subconjunctival filtering surgery show decreased success rates, more complications, and/or more interventions when these surgeries are combined with cataract surgery.[13–20] A recent study utilized the IRIS registry to draw on data from 95,924 trabeculectomies and phaco-trabeculectomies over three years follow-up to find

that stand-alone trabeculectomy and tube shunt procedures resulted in greater IOP reduction compared to combined procedures.[23] Other studies report equivocal surgical outcomes when comparing stand-alone procedures to those combined with phacoemulsification.[7,24–26]

The strongest potential confounder in the present study is the MMC dose distribution. However, this distribution was not significantly different between the three surgical groups and differences in MMC dose did not seem to significantly impact the associated hazard among combined surgery eyes. Further, eyes with previous glaucoma surgery or advanced disease were just as likely to receive a higher or lower dose of MMC (p=0.79 and p=0.87, respectively). In contrast, MMC dose significantly impacted the hazard among refractory and non-refractory stand-alone surgery eyes. The combined eyes were also older, had a slightly higher decision IOP, and an increased frequency of prior trabeculoplasty, though these results do not serve as a better alternative explanation for the additional risk seen. Eleven combined surgeries were performed in refractory eyes. These eyes failed the earliest and most frequently (HR 3.22; 95%CI 1.41 – 7.36) – supporting the additive nature of these two independent risk factors.

In keeping with previous literature,[21,27–29] the intra-operative MMC dose dramatically affected surgical efficacy, needling rates, and complication rates. This effect was not wholly linear or proportional in magnitude. Overall, the observed efficacy difference between MMC doses of 0.2mg/ml and >0.2mg/ml appears to meet an inflection point at six months, which may represent a time in the wound healing process where the effect of the 0.2mg/cc MMC starts to demonstrate a lack of enduring efficacy. Indeed fibroblasts are thought to repopulate the subconjunctival tissues at an accelerated rate when MMC administration is inadequate.[30–32] Alternatively, eyes receiving 0.2mg/ml MMC also underwent needling significantly more frequently – especially during the early post-operatively period. These instances of needling could have delayed surgical failure by several months and produced the inflection point seen at 6-months. Yet overall, variations in fibroblast density, extracellular matrix composition, and stiffness exist between eyes,[33–35] suggesting that different eyes require different concentrations of intraoperative MMC to achieve the same anti-proliferative effect. Employing methods to assess these critical structural risk factors pre-operatively could significantly improve surgical outcomes; however, such methods are yet to be established.

Regarding the overall utility of perioperative MMC, our data suggest a distinct trade-off between efficacy and safety. While surgical success rates significantly improved with MMC doses >0.2 mg/ml (HR 2.2; 95%CI 1.6 – 3.1), the complication rate was also significantly higher (OR 2.2, 95% CI 1.2 – 3.8). However, similar to Beckers et al.,[27] the differential complication rate was driven almost entirely by complications occurring within the first post-operative month, and most were transient and self-limiting. Similar trends are reported in the trabeculectomy literature, with doses of 0.4mg/ml or higher significantly increasing complication rates compared to lower doses,[36–40] whereas doses of 0.2mg/ml have no effect on complication rate compared to lower doses.[41–43] Again, the additional complications associated with higher doses of MMC generally tend to involve post-operative hypotony, small choroidal effusions, and wound leaks – which often are self-limiting in nature and can be addressed through minor post-operative interventions without significantly compromising ultimate surgical success.[37,39]

Combined procedures or those in refractory eyes experienced overall complication rates statistically indistinguishable from those of stand-alone non-refractory eyes. When considering specific types of complications, stand-alone non-refractory eyes had significantly lower rates of macular edema. There was a significantly higher rate of hyphema in refractory eyes – though this is not surprising given these eyes have had previous interventions. Previous studies agree

with these trends and find no significant differences between the complications reported after stand-alone versus combined glaucoma filtering procedures,[18–20] as well as procedures in refractory versus non-refractory eyes.[10]

From an intervention, revision, and reoperation standpoint, fewer differences are seen between the three surgical groups. However, despite the large overall sample size, the relatively low event rate in these categories makes it difficult to derive firm conclusions. The largest difference was the higher needling rate for the combined group (23.3%) and the refractory group (12.8%), relative to the stand-alone group (6.8%). Previous work by Sacchi et al. comparing needling rates after trabeculectomy and phacotrabeculectomy support a differential needling rate and report rates of 45% after phacotrabeculectomy compared to 25% after stand-alone trabeculectomy.[44] Fea et al. similarly report an increased needling rate after phaco-XEN compared to stand-alone XEN procedures.[45] Higher post-operative intervention rates are also reported in refractory eyes undergoing trabeculectomy, with 57% of refractory eyes receiving post-operative interventions compared to only 26% of non-refractory eyes.[46] In the present study, doses of MMC < 0.4mg/ml were also associated with higher needling rates (OR 3.1; 95%CI 1.8 – 5.4), whereas the MMC dose did not impact the frequency of other minor post-operative interventions. Reibaldi et al. revealed a similar trend when comparing trabeculectomy with no MMC to trabeculectomy with 0.2mg/ml MMC, reporting needling rates of 47% and 37% respectively,[41] and this trend is in line with previously published needling rates after SIBS microshunt implantation in refractory eyes, where the hazard ratio (95%CI) for needling associated with receiving < 0.4mg/ml MMC was 4.4 (1.3 – 15.2).[47] These data collectively suggest that higher doses of MMC (>0.2mg/ml) are necessary to reduce the incidence of post-operative bleb needling.

Surgical revisions (4%) for glaucoma occurred relatively infrequently in the presented study, and no significant difference was observed between stand-alone non-refractory procedures (3.8%), combined procedures (4.7%), or for those in refractory eyes (4.0%). A slight trend for increased revisions in combined procedures was evident, although not statistically significant. In line with this trend, Widder et al. reported increased revisions after phaco-XEN compared to stand-alone XEN; however, they employed a shallow threshold to undergo revision surgery (if necessary, instead of restarting glaucoma medications post-operatively, revision surgery was performed) and reported an overall revision rate of 34%.[48] Previous literature suggests an increased revision rate after trabeculectomy in refractory eyes;[10,46] however, these studies are small in size, and their reported differences do not attain statistical significance.

The results of this study are strengthened by its large sample size, minimal lost to follow-up, multi-surgeon academic training environment, and broad inclusion criteria allowing for external generalizability, as well as clinically relevant analyses, including robust risk factor analyses not only for failure but also post-operative medication use, needling, and complications. Based on the primary outcome reported in this study, the maximum survival difference at 12-months occurred between the non-refractory and refractory groups (17%); the sample included in the study (234 stand-alone, 86 combined, and 125 refractory eyes) had a power of 75% for detecting such a difference. However, one limitation of our study is that it may have been underpowered for detecting the survival difference between stand-alone and combined surgery groups (11%), as the sample only had a power of 38% for detecting such a difference. Other limitations of this study include its non-randomized and retrospective nature, opening it up to biases relating to patient selection, indication, selected MMC dose, and non-systematic follow-up and data collection, including differential gaps in follow-up between groups that may delay or

obfuscate post-operative events. However, only 14% of eyes were lost to follow-up, and the gaps in follow-up were minimal, with no significant difference in median follow-up visit interval between study groups suggesting these biases may have had minimal impact on our results.

In conclusion, the efficacy and safety of this SIBS microshunt are reassuring. A striking non-modifiable risk factor for failure includes whether eyes have previously undergone subconjunctival surgery. By and large, whether the surgery is combined with cataract surgery is also non-modifiable. However, there would be situations where cataract surgery is imminent, and there may be latitude to consider a trabecular meshwork bypass MIGS approach in combination with the cataract surgery, reserving the possibility of subconjunctival microshunt surgery for some time in the future, if necessary. Such a stepwise approach is not always possible when there are efficacy concerns for trabecular bypass approaches for that individual patient in the setting of high IOP, advanced disease, high medication load, or difficulty tolerating medications. From a modifiable risk factor perspective, these data present a compelling argument to consider >0.2mg/ml doses of intraoperative MMC for overall higher rates of eyes achieving IOP targets, fewer post-operative medications, and fewer needlings with a somewhat increased rate of albeit mostly transient minor complications occurring primarily within the first post-operative month – which appeared to increase at doses greater then 0.4mg/ml. Another interesting and likely not surprising clinical pearl is that any IOP elevation > 10mmHg within the first post-operative month was associated with surgical failure, post-operative medication use, and a higher needling rate. The validity of this risk factor is supported by the work of Cutolo et al., who report that eyes with IOP elevations > 9mmHg were more than twice as likely to experience surgical failure,[49] and by the work of Schlenker et al., who report over three times the rate of needling in eyes with an IOP elevation > 10mmHg within the first post-operative month.[50] Knowledge of this risk factor will help guide the frequency of monitoring during the post-operative period and prime the surgeon to consider more involved post-operative management plans in eyes with IOP elevations > 10mmHg within the early post-operative period.

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Figure Captions

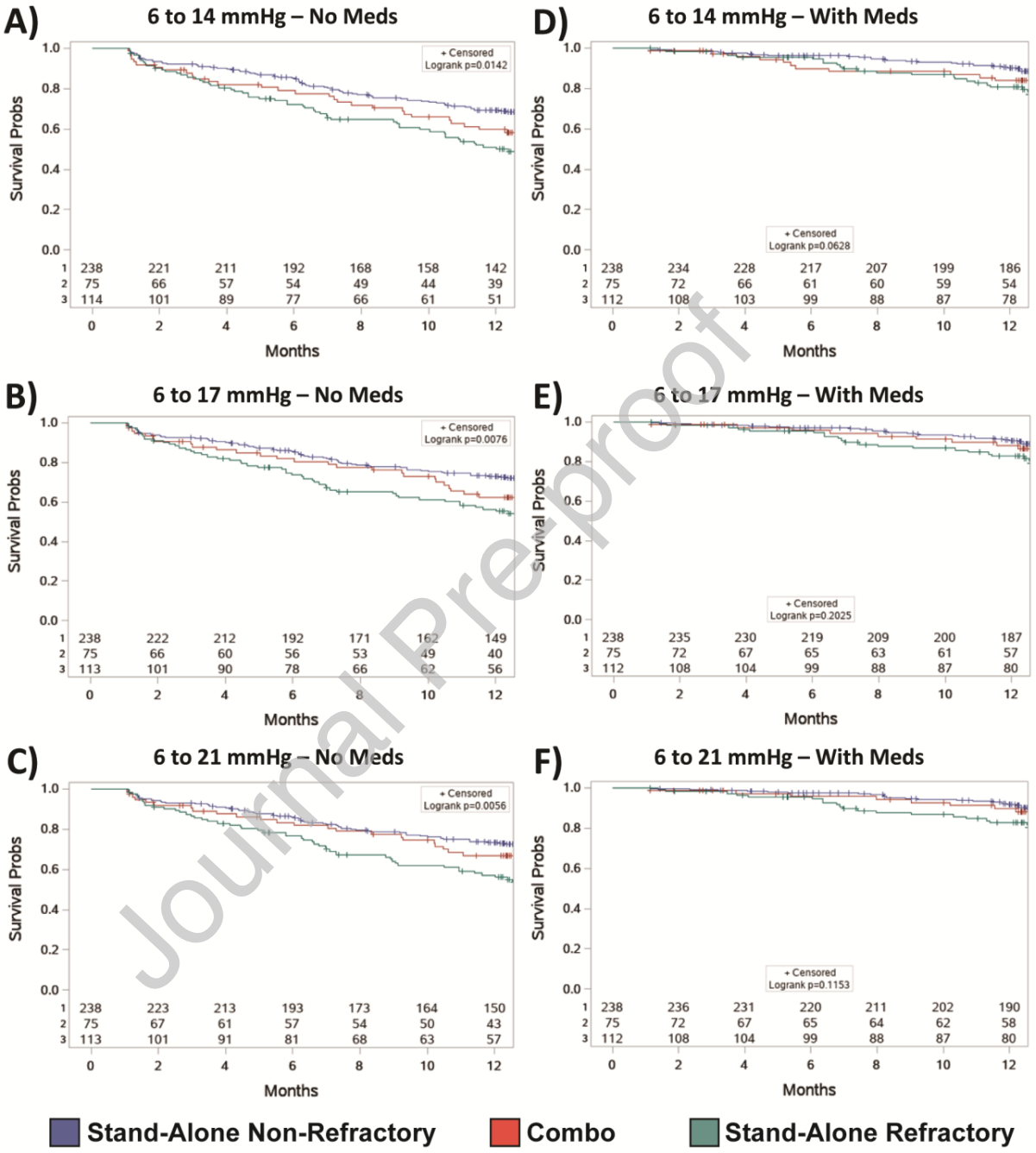

FIGURE 1. Kaplan-Meier survival curves for complete and qualified success through 12 months. Kaplan-Meier survival curves for complete success defined as eyes being medication free, achieving a ≥20% IOPR, and no two IOP measurements above (A) 17 mmHg, (B) 14 mmHg, (C) 21 mmHg without clinical hypotony. (D-F) qualified success. Note: n=11 refractory eyes underwent procedures combined with phacoemulsification.

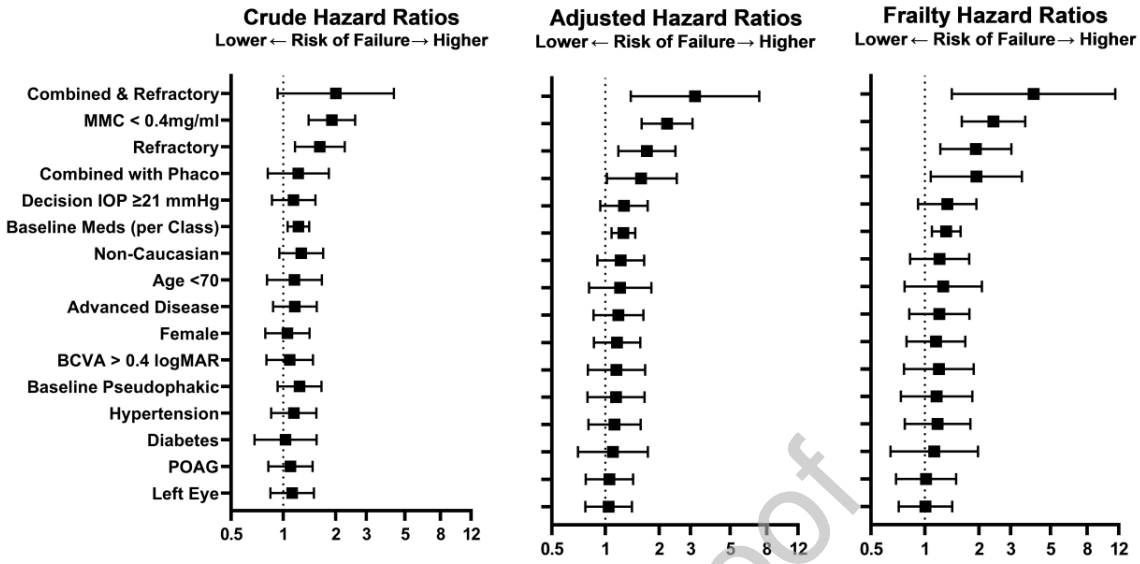

FIGURE 2. Crude and adjusted hazard ratios for surgical failure. Shown are crude (Left) and adjusted (Right) hazard ratios for various risk factors, with 95% confidence intervals. Interaction of surgery type with MMC concentration is shown below. Decision IOP: intraocular pressure at the time surgery was decided. Advanced glaucoma was defined as a mean deviation on visual fields worse than -12 dB. MMC, mitomycin C; POAG, primary open-angle glaucoma.

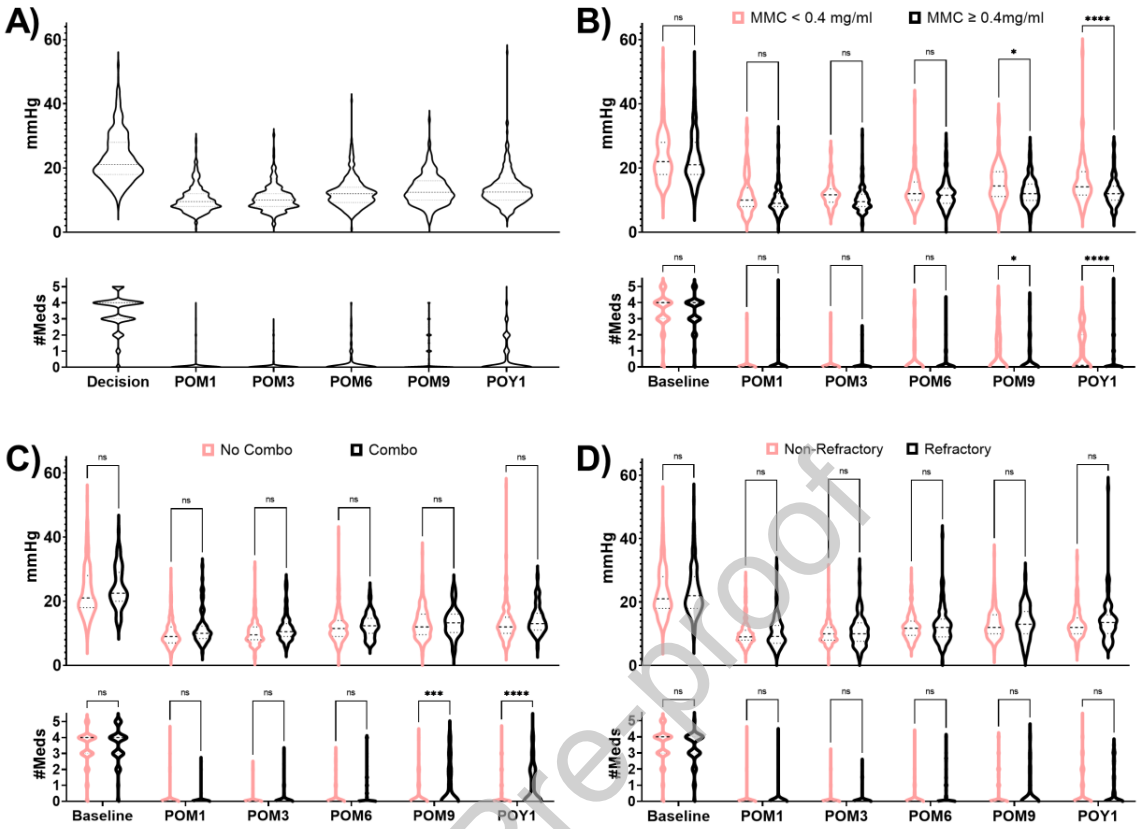

FIGURE 3. Violin plots with median and interquartile ranges of intraocular pressure and medication classes at the time the decision was made to undergo surgery and at the indicated follow-up visit. A) All included eyes, B) those receiving intra-operative MMC ≥0.4mg/ml vs. lower doses, C) combined vs. stand-alone procedures, and D) refractory vs. non-refractory eyes. POM, post-operative month; POY, post-operative year. Width of the violin plots represents the proportion of eyes at a given y-value at each follow-up visit.

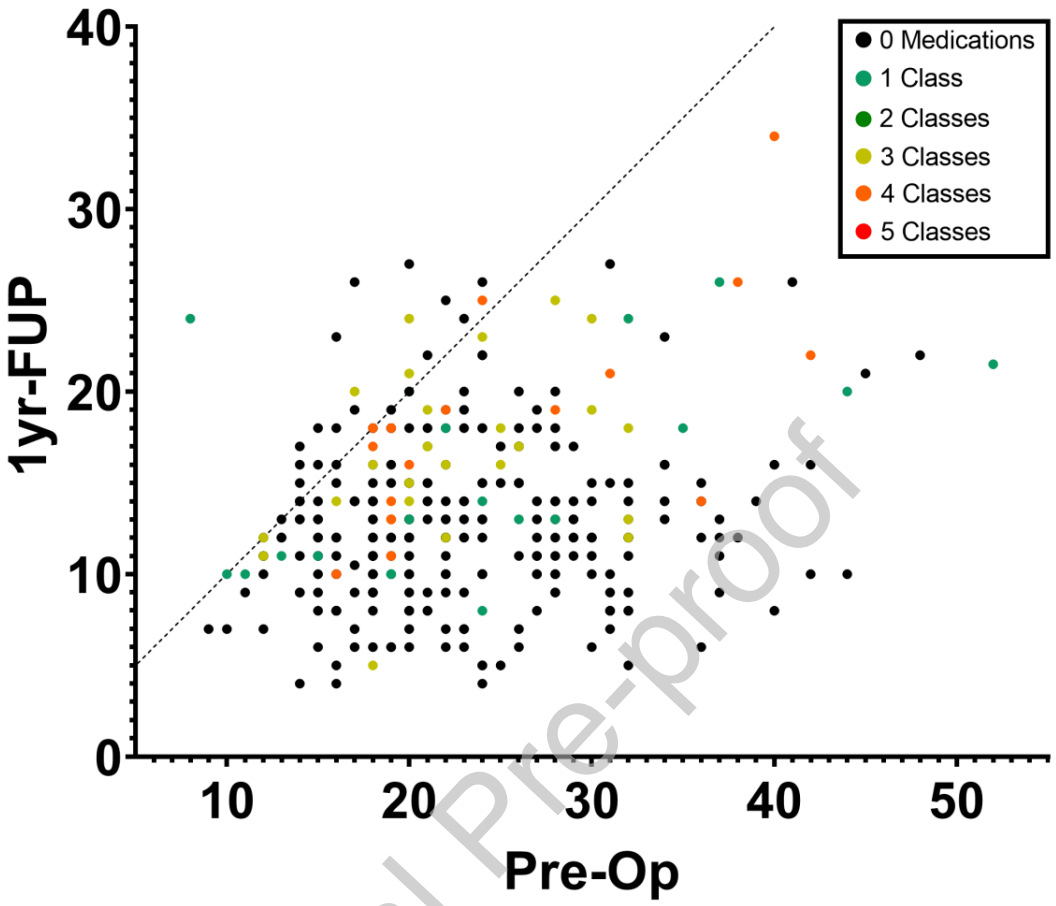

FIGURE 4. Scatterplot of intraocular pressure (IOP) at the time of surgical decision (x-axis) vs the IOP at post-operative year three (1yr FUP; y-axis). The points represented are measurements taken at the closest visit to 12 months postoperatively between 10 months and 14 months. Eyes without available data in this range were not represented in this chart. The color of the data point represents a patient's medication requirement at 1 year. Data points plotted along the dotted line represent no change in IOP from the time surgery was decided to post-operative month 12, and all those under the dotted line represent a reduction from the decision IOP.

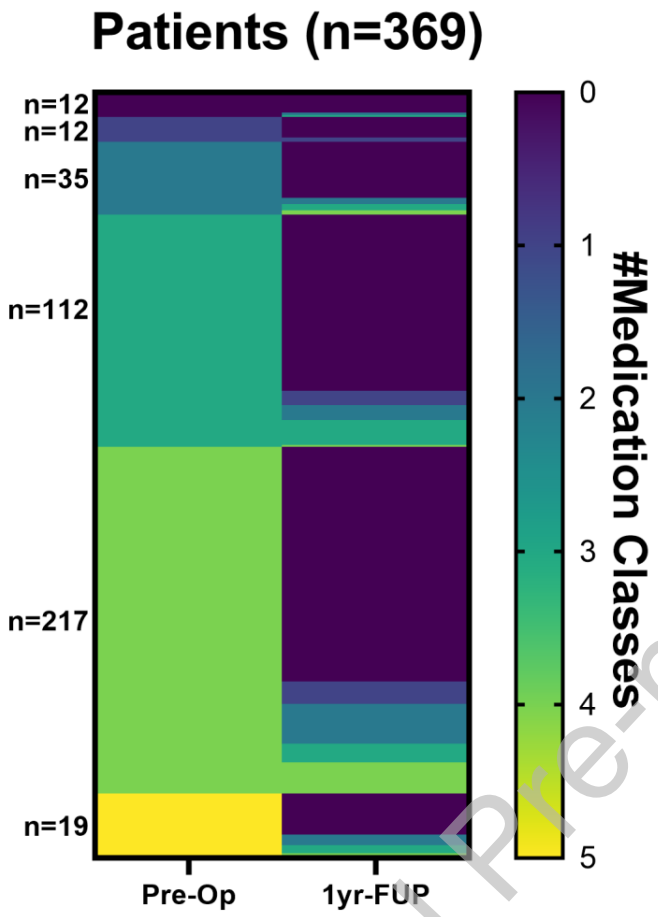

FIGURE 5. Heatmap representing the percentage of patients' eyes on 0-5 glaucoma medication classes at the time of surgical decision and at post-operative year 1.

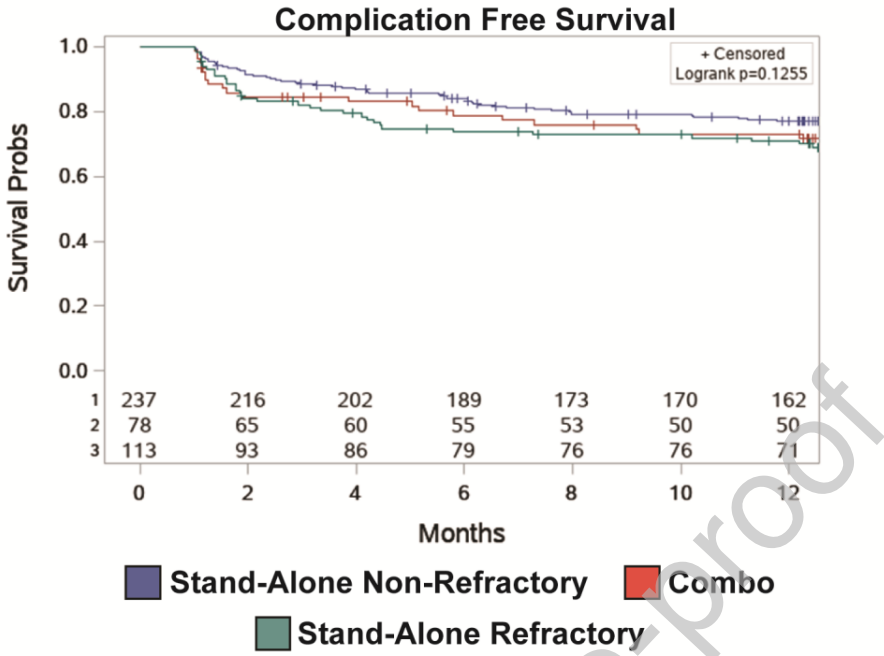

FIGURE 6. Kaplan-Meier survival curve for post-operative complications stratified by non-refractory stand-alone, non-refractory combined, and refractory stand-alone.

FIGURE S1. Kaplan-Meier survival curve for the proportion of eyes maintaining a medication free post-operative course stratified by eyes with and without a single IOP measured ≥ 10 mmHg during the first post-operative month.

FIGURE S2. A) Crude and adjusted hazard ratios for post-operative bleb needling. Shown are crude (Left) and adjusted (Right) hazard ratios for various risk factors, with 95% confidence intervals. B) Kaplan-Meier curve for post-operative needling stratified by MMC ≥ 0.4mg/ml.

Table 1: Baseline Characteristics of Subjects Receiving Microshunt	
Demographic	Patients, N=376; eyes, n=436
Age, Median (IQR), years	61 (52-69)
>70 years, n (%)	93 (21%)
Left eye, n (%)	209 (48%)
Female, n (%)	186 (43%)
Diabetes, n (%)	63 (14%)
Non-Caucasian	233 (53%)
Vision	
Preop VA (logMAR), median (IQR)	0.3 (0.1-0.48)
Preop BCVA ≥0.4 logMAR, n (%)	125 (29%)
Glaucoma type and severity	
Decision IOP, median (IQR)[1]	21 (18-28)
Medication classes, median (IQR)	4 (3-4)
Cup-to-disk ratio, median (IQR)	0.9 (0.8-0.9)
Preop MD, median (IQR), dB	-10.8 (-20.8 to -3.9)

Table 2: Microshunt Eyes with Postoperative Complications

Disease type	
POAG, n (%)	255 (58%)
PXG, n (%)	35 (8%)
OAG, n (%)	98 (22%)
ACG, n (%)	9 (2%)
NTG, n (%)	15 (3%)
OHTN, n (%)	2 (0.5%)
Other Glaucoma, n (%)	23 (5%)
Disease severity, n (%)[2]	
Mild	96 (22%)
Moderate	85 (19%)
Advanced	257 (59%)
Previous ocular laser/surgery, n (%)	
Previous Subconjunctival Surgery	127 (29%)
Trabeculectomy, n (%)	45 (10%)
Tube Shunt, n (%)	42 (11%)
XEN, n (%)	22 (6%)
Cypass, n (%)	11 (3%)
Other Sub. Conj. n (%)	7 (2%)
CPC, n (%)	12 (3%)
Laser trabeculoplasty, n (%)	216 (49%)
Trabeculotomy / Trab. Stents, n (%)	14 (3%)
Prev. Cataract surgery, n (%)	168 (38%)
Surgical Details, n (%)	
Combined w/Cataract Surgery	86 (19%)
MMC 0.2 mg/mL	96 (22%)
MMC 0.4 mg/mL	210 (48%)
MMC 0.5 mg/mL	130 (30%)

BCVA=best-corrected visual acuity; IOP = intraocular pressure; IQR = interquartile range; logMAR = logarithm of the minimum angle of resolution; MD = mean deviation; MMC = mitomycin C; OAG = open-angle glaucoma; VA = visual acuity. OAG=PXG, PDS, CMG, JOAG. Other Glaucoma=NVG, Elevated EVP, Traumatic, Uveitic. [1]IOP measured at the visit when the decision was made to proceed with surgery. [2]Based on visual field mean deviation: mild = 0 dB to > -6 dB; moderate = -6 dB to > -12 dB; and advanced = -12 dB or worse

Subconjunctival Microshunt 1-year Outcomes and Risk-Factors

Complication	Stand-Alone, Non-Refractory, N=183 (eyes, n=234)			Combined, N=73 (eyes, n=86)			Refractory, N=119 (eyes, n=127)			p-value (for total)
	Total	Early (<1mo)	Late (≥1mo)	Total	Early (<1mo)	Late (≥1mo)	Total	Early (<1mo)	Late (≥1mo)	
Minor, n (%)	64 (27%)	40 (17%)	34 (15%)	27 (31%)	16 (19%)	11 (13%)	43 (34%)	25 (20%)	18 (14%)	0.43
Choroidal	22 (9%)	16 (7%)	6 (3%)	12 (14%)	9 (11%)	3 (4%)	14 (11%)	14 (11%)	-	0.5
Hyphema	16 (7%)	15 (6%)	1 (0.5%)	1 (1%)	1 (1%)	-	14 (11%)	14 (11%)	-	0.01
Shallow AC	16 (7%)	14 (6%)	2 (1%)	11 (13%)	8 (9%)	3 (4%)	9 (7%)	8 (6%)	1 (1%)	0.2
Diplopia	14 (6%)	1 (0.4%)	13 (6%)	3 (4%)	-	3 (4%)	-	-	-	0.02
Bleb Encapsulation	7 (3%)	5 (2%)	2 (1%)	5 (6%)	5 (6%)	-	4 (3%)	4 (3%)	-	0.47
Iridocorneal touch	7 (3%)	7 (3%)	-	5 (6%)	3 (4%)	2 (2%)	4 (3%)	3 (2%)	1 (1%)	0.47
Hypot. Maculopath.	7 (3%)	2 (1%)	5 (2%)	3 (4%)	-	3 (4%)	10 (8%)	1 (1%)	9 (7%)	0.08
Leak/dehiscence	5 (2%)	2 (1%)	3 (1%)	6 (7%)	2 (2%)	4 (5%)	3 (2%)	1 (1%)	2 (2%)	0.07
Blocked lumen	5 (2%)	1 (0.4%)	4 (2%)	4 (5%)	2 (2%)	2 (2%)	1 (1%)	1 (1%)	-	0.18
Macular edema	4 (2%)	1 (0.4%)	3 (1%)	4 (5%)	-	4 (5%)	9 (7%)	0	9 (7%)	0.03
Ptosis	4 (2%)	-	4 (2%)	4 (5%)	-	4 (5%)	2 (2%)	-	2 (2%)	0.25
Corneal edema	3 (1%)	-	3 (1%)	1 (1%)	-	1 (1%)	6 (5%)	1 (1%)	5 (4%)	0.07
Iritis	3 (1%)	-	3 (1%)	3 (4%)	1 (1%)	2 (2%)	4 (3%)	-	4 (3%)	0.35
VH	2 (1%)	2 (1%)	-	-	-	-	1 (1%)	1 (1%)	-	0.7
Tube migration	1 (0.4%)	-	1 (0.4%)	-	-	-	-	-	-	0.63
Serious, n (%)										
Microshunt erosion	-	-	-	1 (1%)	-	1 (1%)	-	-	-	0.3
Endophthalmitis	-	-	-	-	-	-	1 (1%)	1 (1%)	-	0.28
MG	-	-	-	2 (2%)	2 (2%)	-	-	-	-	0.02
No light perception	1 (0.4%)	-	1 (0.4%)	-	-	-	-	-	-	0.69

AC: anterior chamber; VH: vitreous hemorrhage; MG: malignant glaucoma

Table 3: Microshunt Eyes with Postoperative Interventions

Intervention	Stand-Alone, Non-Refractory, N=183 (eyes, n=234)	Combo, N=73 (eyes, n=86)	Refractory, N=119 (eyes, n=127)	Chi Square p-value
Any Intervention	32 (13.7%)	24 (27.9%)	26 (20.8%)	0.01
Needling	16 (6.8%)	20 (23.3%)	16 (12.8%)	0.0002
MMC Injection	14 (6%)	11 (12.8%)	4 (3.2%)	-
OVD Injection	9 (3.8%)	9 (10.5%)	3 (2.4%)	-
5-FU Injection	1 (0.4%)	1 (1.2%)	-	-
Anterior chamber reformation	12 (5.1%)	8 (9.3%)	11 (8.8%)	0.31
Anterior chamber tap	6 (2.6%)	2 (2.3%)	5 (4.0%)	0.73

Choroidal Drainage	-	-	1 (0.8%)	-
Abbreviations: IOP, intraocular pressure; OR, odds ratio; MMC, Mitomycin C; OVD, ophthalmic viscoelastic device; 5-FU, 5-Fluorouracil.				

Table 4: Eyes with Postoperative Revisions and Reoperations

Procedure	Stand-Alone, Non-Refractory, N=183 (eyes, n=234)	Combo, N=73 (eyes, n=86)	Refractory, N=119 (eyes, n=127)	Chi Square p-value
Any Revision	9 (3.8%)	4 (4.7%)	5 (4.0%)	0.95
Ab externo Bleb Revision	8 (3.4%)	4 (4.7%)	5 (4.0%)	-
Device Exchange	7 (3.0%)	3 (3.5%)	-	-
Any Reoperation	3 (1.3%)	-	3 (2.4%)	0.33
Ahmed Glaucoma Valve	2 (0.9%)	-	-	-
Baerveldt glaucoma implant	1 (0.4%)	-	-	-
CPC	-	-	2 (1.6%)	-
Enucleation	1 (0.4%)	-	-	-
Abbreviations: IOP, intraocular pressure; OR, odds ratio.				

Subconjunctival Microshunt 1-year Outcomes and Risk-Factors

Table of Contents Statement - Precis

Over 1-year of follow-up, the SIBS microshunt adequately controlled IOP without the need for glaucoma medications in 75% of non-refractory patients undergoing stand-alone procedures, in 64% of patients undergoing procedures combined with phacoemulsification, and in 58% of refractory patients undergoing stand-alone procedures. With the use of postoperative medications, success was achieved in 93%, 91%, 85%, respectively. Overall, 47% of patients were medication free at last follow up, and only 12% required needling.

Declaration of interests

☐ The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

☒The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

MBS has received consulting fees and honoraria from Santen. IIA has received non-financial support, research grant support, consulting fees and honoraria from Santen and Glaukos.