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ORIGINAL RESEARCH

MIGS in Severe Glaucoma: 12-Month Retrospective Efficacy and Safety of Microinvasive Glaucoma Surgery with Cataract Extraction

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Purpose: Despite holding promise, reports of using MIGS in severe glaucoma are scarce, and none has described combining multiple MIGS in this population. To the best of our knowledge, this is the largest study to report outcomes of phacoemulsification and MIGS (Phaco/MIGS) in patients with severe glaucoma.

Methods: This retrospective review comprised 327 clinical visits of 71 patients with severe glaucoma who underwent Phaco/MIGS with iStent, endocyclodestruction, Kahook Dual Blade, Hydrus Microstent, or a combination of these MIGS (cMIGS) performed between 2016 and 2021. Primary outcomes included intraocular pressure (IOP) and medication burden evaluated by Generalized Estimating Equations, as well as Kaplan–Meier Estimates. Further analyses compared the efficacy of cMIGS and single Phaco/MIGS (sMIGS), procedure duration, visual acuity, and complications.

Results: Mean preoperative IOP was 16.7 mmHg ± 5.8 (SD) on 2.3 ± 1.9 medications overall (N = 71), 16.9 ± 6.3 mmHg on 1.7 ± 1.9 medications in the sMIGS group (N = 37), and 16.4 ± 5.3 mmHg on 2.9 ± 1.6 medications in the cMIGS group (N = 34). Throughout 12 months, Phaco/MIGS led to significant reduction patterns in IOP ($p < 0.001$) and medications ($p = 0.03$). At 12 months, 47.5%, 87.5%, and 64.7% of the patients achieved IOP ≤ 12 mmHg, 17 mmHg, or predetermined goal IOP, respectively, without additional medication or procedure. Mean 12-month IOP was 13.5 ± 3.1 mmHg on 1.8 ± 1.7 medications. After adjusting for baseline medication burden, the reduction pattern in IOP ($p < 0.05$) was different between cMIGS and sMIGS, favoring cMIGS, and the groups had similar reduction patterns in medications ($p = 0.75$).

Conclusion: The use of Phaco/MIGS in patients with cataract and severe glaucoma may significantly reduce IOP and medication burden throughout 12 months and, thus, may serve as a stepping stone in severe glaucoma patients with visually significant cataract before proceeding with more invasive glaucoma surgery. This effect may be potentiated by the combination effect of cMIGS.

Plain Language Summary: Many patients with cataract and mild or moderate glaucoma who undergo cataract surgery also benefit from microinvasive glaucoma surgery (MIGS) performed at the same time, but the role of MIGS in patients with severe glaucoma and cataract is not clear. We report that combined cataract surgery and MIGS were associated with significant reductions in eye pressure in patients with severe glaucoma for more than 12 months.

Keywords: microinvasive glaucoma surgery, MIGS, cMIGS, combined MIGS, generalized estimating equations, GEE, comparative effectiveness, combined efficacy, severe glaucoma

Introduction

Microinvasive glaucoma surgery (MIGS) has been shown to decrease intraocular pressure and medication burden in primary open-angle glaucoma patients for up to 2 years after surgery.[1–6] Despite this, its efficacy in severe stage disease is not well established and is currently performed as an off-label intervention.[1,7] Characterized by an ab-interno approach

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and minimal disruption to angle anatomy, MIGS is increasingly applied in mild-to-moderate glaucoma, filling a gap in a more established treatment paradigms of antiglaucoma medications, laser procedures, and filtration surgeries. While trabeculectomy and glaucoma drainage implants effectively reduce intraocular pressure (IOP) and progression of glaucomatous damage and vision loss, the invasive approaches are associated with a number of complications even years after surgery, including reduced visual acuity, hypotony, hyphema, suprachoroidal hemorrhage, blebitis, endophthalmitis, leak or device exposure, and up to a 33% failure rate within 3 years.[1,8,9] In contrast and despite more modest efficacy, MIGS has been reported with a promising safety profile compared to filtering surgeries, including reduced complication rates, reduced surgical time, shorter postoperative recovery time, and higher biocompatibility.[1] The promising safety and recovery profile of MIGS has been compelling and has led to frequent pairing with cataract surgery (Phaco/MIGS).[1–7,9] However, the efficacy of MIGS in patients with both severe glaucoma and visually significant cataract is poorly understood.

In a recent review study of 3476 eyes, increased glaucoma severity was associated with a higher reoperation rate following MIGS, and Dr. Ike Ahmed and other authors posit that patients with severe glaucoma may require more interventions to reach a lower target IOP.[1] In fact, with many different mechanisms of action among MIGS, there is a growing interest in establishing whether combining multiple MIGS (cMIGS) leads to an additive or synergistic effect.[10–12]

This observational retrospective cohort study investigates the efficacy and safety of Phaco/MIGS in patients with both severe glaucoma and cataract, as well as comparative outcomes of single MIGS versus combined MIGS in this population. We stage severe glaucoma according to the ICD-10 guidelines requiring both optic nerve abnormalities consistent with glaucoma and also glaucomatous visual field abnormalities in both hemifields and/or loss within 5 degrees of fixation in at least one hemifield.[13] Because of the small number of off-label MIGS surgeries performed on patients with severe glaucoma, we include both procedures that improve trabecular drainage and that reduce aqueous humor production.

To improve trabecular drainage, phacoemulsification is frequently combined with ab-interno trabecular excision using the Kahook Dual Blade (KDB; New World Medical, CA, USA). Relying on retrospective studies and case series, the efficacy of Phaco/KDB has been reported with 12-month IOP reductions between 1.9 and 11.7 mmHg.[1,13–23]

Hydrus Microstent (Ivantis Inc., CA, USA) offers a dual mode of action by stenting Schlemm's canal and bypassing the trabecular meshwork. When performed with phacoemulsification (Phaco/Hydrus), Hydrus Microstent insertion reduced mean washed out diurnal IOP by 9.4 mmHg at 2 years postoperatively in HYDRUS II, a multi-center, prospective, single-masked, randomized controlled clinical trial.[24] The efficacy of Phaco/Hydrus has been more modest in subsequent studies, with 12-month medicated IOP reductions ranging between 1.7 and 3.9 mmHg in the literature.[1,25–28]

Acting to reduce aqueous humor production rather than increase aqueous drainage, endocyclophotocoagulation (ECP; Endo Optiks, BVI, MA, USA) is an ab-interno cyclodestructive procedure where ciliary body processes are ablated under endoscopic visualization. At 12 months after phacoemulsification combined with ECP (Phaco/ECP), mean IOP has been reported to be reduced by 2.7 to 11.5 mmHg in retrospective studies.[11,29] Although complications including intraocular pressure spikes, postoperative anterior chamber inflammation, and lens dislocation remain concerns, the procedure has an established safety profile, especially for mild and moderate glaucoma.[30–32]

Leveraging multiple mechanisms of action, the combination of phacoemulsification, ECP, and KDB (PEcK) has been associated with reductions in mean intraocular pressure between 3.8 and 5.5 mmHg.[10,11,33,34] PEcK may confer greater IOP reduction without added procedural time compared to its constituent sMIGS Phaco/ECP and Phaco/KDB in populations with predominantly mild or moderate glaucoma.[11,33] In retrospective studies of predominantly mild or moderate glaucoma, PEcK has also been compared to another cMIGS procedure combining trabecular microbypass by iStent insertion, Cataract extraction, and ECP (ICE1 for iStent G1 or ICE2 for iStent infinite). At 12 months, the studies reported greater mean IOP reduction following PEcK compared to ICE (5.0 to 5.1 mmHg and 2.3 to 3.1 mmHg, respectively), as well as similar or greater mean medication reduction (1.4 to 1.6 fewer medications and 1.0 fewer medications, respectively).[12,34]

This study reports on the efficacy and safety of Phaco/MIGS in patients with both cataract and severe glaucoma and establishes outcomes of combining MIGS for the first time in a population with severe glaucoma.

Methods

Overview

The study protocol was approved by the Massachusetts General Brigham Institutional Review Board. All research adhered to the Declaration of Helsinki and the Health Insurance Portability and Accountability Act. The study protocol and waiver of consent for retrospective chart review was approved by the Massachusetts General Brigham Institutional Review Board (IRB Number 2019P002735).1

Population

Subjects were queried from all surgical records at Massachusetts Eye and Ear performed by a glaucoma specialist between January 2016 and July 2021 and were included if the operative report confirmed having undergone phacoemulsification combined with iStent (Glaukos Corp., CA, USA), endocyclodestruction (Endo Optiks BVI, MA, USA), Kahook Dual Blade (New World Medical, CA, USA), Hydrus Microstent (Ivantis Inc., CA, USA), or a combination of these MIGS. Patients were excluded from the analysis if they were not staged as severe glaucoma at or before their preoperative visit, according to the ICD-10 guidelines where severe glaucoma is defined as both optic nerve abnormalities consistent with glaucoma and also glaucomatous visual field abnormalities in both hemifields and/or loss within 5 degrees of fixation in at least one hemifield.[13] Patients were also excluded if they had an additional procedure performed at the time of surgery, were less than 18 years of age at the time of surgery or had a history of MicroPulse Trans-Scleral Cyclophotocoagulation (MPCPC) in the operative eye. Additionally, patients were excluded from analysis if they had less than 6 weeks of follow-up to avoid biasing data by ignoring early failures in survival analysis. If both eyes of a patient underwent an operation, only the first operated eye was included.

Surgical Technique

For ICE2, PEcK, and Phaco/ECP, standard phacoemulsification was followed by insertion of the ECP probe into the sulcus, and 120–300 degrees of ciliary processes were treated in continuous wave mode at a power of 0.15–0.50 Watts until observing whitening and shrinkage of ciliary processes.

After ECP for ICE2 or PEcK and after standard phacoemulsification for other procedures, the patient's head was rotated for visualization, additional cohesive viscoelastic was inserted into the anterior chamber, and the gonioscopy lens was placed onto the cornea. For ICE2, the first and second iStent inject were inserted into the nasal trabecular meshwork (TM). For PEcK and Phaco/KDB, the KDB was introduced into the anterior chamber and an ab-interno trabecular excision was performed. The KDB was passed through the TM between 2.0 and 5.0 clock hours in an inside out fashion until two strips of TM were formed. For Phaco/Hydrus, the Hydrus Microstent was inserted into the trabecular meshwork (TM) and noted to be in good position. Upon completion of all procedures, a drop of prednisolone and antibiotic were placed on the eye before it was shielded.

Data Collection

Baseline characteristics were collected from electronic health records of subjects and included age, gender, preferred language, race/ethnicity, glaucoma type, and best corrected distance visual acuity (CDVA). Glaucoma type was denoted to be mixed mechanism when there was more than one etiology of glaucomatous disease was documented. Baseline medication burden was recorded as the number of medications prescribed, including the number of constituent agents if fixed-dose combination medications were used. Baseline IOP was defined as the mean of measurements made by the surgeon using Goldmann applanation tonometry on two consecutive visits prior to surgery. If Goldmann applanation tonometry was not available for a pre- or postoperative visit, measurements from an iCare tonometer (Tiolat Oy, Helsinki, Finland) or an Optical Response Analyzer (Reichert Ophthalmic Instruments, Inc., Buffalo, NY, USA) were recorded. Glaucoma stage was recorded and assigned based on the American Academy of Ophthalmology Preferred

Practice Pattern guidelines (ICD-10 Glaucoma Reference Guide).[13] Prior history of ocular surgery, laser peripheral iridotomy (LPI), and laser trabeculoplasty (LTP) in the operative eye was recorded. Prior LTP included Laser Trabeculoplasty (LTP), Argon Laser Trabeculoplasty (ALT), or Selective Laser Trabeculoplasty (SLT). The IOP goal was a preoperatively designated target that corresponded to a 20% IOP reduction from the level at which glaucoma progression was documented.[34]

Postoperative data were collected from 1 day, 6 (±2.5) weeks, 3 (±1) months, 6 (±2) months, 12 (±3) months, 18 (±3) months, 24 (±3) months, 36 (±3) months, 48 (±3) months, and 60 (±3) months. Recorded measurements included IOP, CDVA, number of glaucoma medications, and presence of postoperative complications. If subjects any required further glaucoma procedures, this was recorded. If a patient underwent an additional glaucoma surgery or LTP on the operative eye, a follow-up was concluded at the time. Data was deidentified utilizing the safe harbor method.

Outcomes

Primary outcomes were a pattern of change in intraocular pressure (IOP) and medication burden for 12 months postoperatively, as well as survival analyses. We examined three survival criteria, without receiving additional glaucoma procedure or medication:

- Survival Criteria 12 (SC12): IOP ≤ 12 mmHg.
- Survival Criteria 17 (SC17): IOP ≤ 17 mmHg.
- Survival Criteria goal (SCgoal): IOP ≤ goal IOP, where goal IOP represented a preoperatively designated 20% reduction from the level at which glaucoma progression occurred.

In addition to additional glaucoma procedure or medication, failure included demonstrated inability to meet IOP reductions ≥2 consecutive visits to avoid confounding from temporary intraocular pressure fluctuations. Secondary outcomes included comparison of sMIGS and cMIGS, as well as the pattern of change in the Logarithm of the Minimum Angle of Resolution (logMAR), the procedure length, and incidence of postoperative complications.

Statistical Analysis

Statistical analyses were performed using R statistical programming software (RStudio 2023.12.0). A number of medications and logMAR were treated as continuous variables. Statistical differences in baseline characteristics between cohorts was evaluated by Kruskal–Wallis rank sum tests and Pearson's chi-squared tests.[35,36]

Generalized Estimating Equations (GEE) were used to assess both the magnitude and temporality of change and to properly account for repeated outcome measurements.[37,38] Additionally, GEEs are often suggested as the preferred model type for interpreting population findings for continuous variables of repeated measurements without known distributions and with a small sample size.[39] Through GEEs, semi-parametric longitudinal regression models were fit to each outcome, including IOP, medication burden, and logMAR. Models were examined between procedures and across each categorical timepoint throughout 12 months. For selected baseline characteristics that were significantly or near significantly different between procedures, the respective variables were included in the models for adjustment of these differences. Statistical significance of covariates within the models was evaluated using Wald tests, which resulted in a single p-value that compares the pattern of change across all timepoints, between procedures, or under both conditions, while holding all other covariates constant. Kaplan–Meier survival probabilities were generated and are presented as plots of event-free survival overall and stratified by cMIGS and sMIGS. Statistical difference in the pattern of survival was evaluated using Log rank tests.[40]

Results

Baseline Characteristics

Three hundred and twenty-seven visits from 71 eyes of 71 patients were included. The mean preoperative IOP was 16.7 mmHg ± 5.8 (SD) on 2.3 ± 1.9 medications overall (N = 71), 16.9 ± 6.3 mmHg on 1.7 ± 1.9 medications in the sMIGS

Table 1 Baseline Characteristics

Variable	Overall, N = 71	sMIGS, N = 37	cMIGS, N = 34	p-value
Demographic Characteristics				
Age at surgery, mean (SD) [years]	72.46 (9.24)	73.32 (9.90)	71.52 (8.52)	0.49
Female sex, N (%)	34 (48%)	19 (51%)	15 (44%)	0.71
Race-Ethnicity, N (%)				0.39
White	37 (52%)	21 (57%)	16 (47%)	
Black or African American	16 (23%)	8 (22%)	8 (24%)	
Hispanic or Latino	6 (8.5%)	3 (8.1%)	3 (8.8%)	
Asian	2 (2.8%)	1 (2.7%)	1 (2.9%)	
Other	4 (5.6%)	0 (0.0%)	4 (12%)	
Declined	6 (8.5%)	4 (11%)	2 (5.9%)	
Non-English speaker, N (%)	15 (21%)	8 (22%)	7 (21%)	>0.99
Glaucoma Characteristics				
IOP, mean (SD) [mmHg]	16.66 (5.81)	16.93 (6.32)	16.37 (5.27)	0.74
IOP ≤ 12 mmHg, N (%)	15 (21.1%)	7 (18.9%)	8 (23.5%)	
IOP ≤ 17 mmHg, N (%)	49 (69.0%)	25 (67.6%)	24 (70.6%)	
IOP ≤ goal IOP, N (%)	21 (29.6%)	12 (32.4%)	9 (26.5%)	
Number of glaucoma medications, mean (SD)	2.28 (1.85)	1.68 (1.87)	2.94 (1.61)	0.002*
Glaucoma Type, N (%)				0.87
Primary Open Angle	47 (66%)	25 (68%)	22 (65%)	
Mixed mechanism	12 (17%)	6 (16%)	6 (18%)	
Pseudoexfoliation	6 (8.5%)	3 (8.1%)	3 (8.8%)	
Pigmentary	1 (1.4%)	0 (0.0%)	1 (2.9%)	
Normal or Low Tension	5 (7.0%)	3 (8.1%)	2 (5.9%)	
Prior laser trabeculoplasty[a] on operative eye, N (%)	17 (24%)	9 (24%)	8 (24%)	>0.99
Prior LPI on operative eye, N (%)	9 (13%)	5 (14%)	4 (12%)	>0.99
Other Ocular Characteristics				
Best corrected distance VA LogMAR, mean (SD) [log unit]	0.41 (0.47)	0.41 (0.32)	0.41 (0.59)	0.14
Prior surgery on operative eye, N (%)				0.71
Non-Functioning Glaucoma Drainage Implant	3 (4.2%)	2 (5.4%)	1 (2.9%)	
Scarred-Down Trabeculectomy	3 (4.2%)	1 (2.7%)	2 (5.9%)	
Iridectomy	1 (1.4%)	0 (0.0%)	1 (2.9%)	
Corneal	1 (1.4%)	1 (2.7%)	0 (0.0%)	
Retinal	3 (4.2%)	2 (5.4%)	1 (2.9%)	
None	60 (85%)	31 (84%)	29 (85%)	
Procedure Characteristics				
Procedure duration, mean (SD) [minutes]	40.61 (11.42)	41.16 (10.93)	40.00 (12.06)	0.56
Procedures with Kahook Dual Blade, N (%)	45 (63.4%)	13 (35.1%)	32 (94.1%)	—
Clock hours incised by KDB, mean (SD)	3.72 (0.66)	3.21 (0.76)	3.92 (0.51)	<0.001*
Procedures with Endocyclophotocoagulation, N (%)	49 (69%)	15 (40.5%)	34 (100%)	—
Degrees of ECP, mean (SD) [degrees]	210.33 (40.61)	227.14 (53.70)	202.97 (31.64)	0.12

(*Continued*)

Table 1 (Continued).

Variable	Overall, N = 71	sMIGS, N = 37	cMIGS, N = 34	p-value
Power of ECP, mean (SD) [W]	0.33 (0.07)	0.29 (0.09)	0.35 (0.06)	0.06
Procedures with Hydrus Microstent, N (%)	9 (12.7%)	9 (24.3%)	0 (0%)	—
Procedures with iStent infinite, N (%)	2 (2.8%)	0 (0%)	2 (5.9%)	—

Notes: Baseline demographics, disease characteristics, and procedural history in subjects who underwent phacoemulsification with single or combined MIGS (sMIGS or cMIGS respectively). Kruskal–Wallis rank sum tests and Pearson's Chi-squared tests with significance defined as $p < 0.05$ (*). [a]Laser trabeculoplasty includes Laser Trabeculoplasty (LTP), Argon Laser Trabeculoplasty (ALT), or Selective Laser Trabeculoplasty (SLT).
Abbreviations: ECP, Endocyclophotocoagulation; IOP, Intraocular pressure; KDB, Kahook Dual Blade; LPI, Laser Peripheral Iridotomy; VA, visual acuity.

group (N = 37), and 16.4 ± 5.3 mmHg on 2.9 ± 1.6 medications in the cMIGS group (N = 34) (Table 1). The preoperative IOP was ≤12 mmHg, 17 mmHg, or predetermined goal IOP in 21.1%, 69.0%, and 29.6% of the patients, respectively. The subjects had a mean age of 72.46 years and were largely naïve to surgery (85%).

Patients who underwent sMIGS were statistically similar to those who underwent cMIGS based on age, sex, race-ethnicity, proportion of non-English speakers, baseline IOP, glaucoma type, prior glaucoma procedures, and preoperative best corrected distance visual acuity (Table 1). However, patients who underwent cMIGS were on more medications at baseline compared to those who underwent sMIGS ($p = 0.002$).

Comprising ICE2 and PEcK, cMIGS procedures performed ECP similarly to the sMIGS Phaco/ECP, but cMIGS approached significant difference with higher power ($p = 0.12$) over a smaller range of ciliary bodies ($p = 0.06$) compared to sMIGS. In terms of goniotomy with Kahook Dual Blade, surgeons incised a greater number of trabecular meshwork clock hours when performing the cMIGS procedure, PEcK, compared to that with the sMIGS, Phaco/KDB ($p < 0.001$). Baseline characteristics stratified by individual procedure types are included in Supplemental Table 1.

Procedural and Comparative Efficacy

For 12 months, all procedures resulted in significant patterns of reduction in IOP ($p < 0.001$) and in medication burden ($p = 0.03$) (Tables 2 and 3). The mean IOP was reduced to 13.5 ± 3.6 mmHg on 1.8 ± 1.7 medications at 12 months postoperatively.

Table 2 Change in Intraocular Pressure

Outcome: IOP [mmHg]	Overall		sMIGS		cMIGS	
	N	Mean (SD)	N	Mean (SD)	N	Mean (SD)
Baseline	71	16.7 (5.8)	37	16.9 (6.3)	34	16.4 (5.3)
6 weeks	67	13.0 (3.8)	35	13.2 (3.9)	32	12.8 (3.8)
3 months	46	12.4 (3.9)	24	13.0 (4.0)	22	11.8 (3.8)
6 months	51	13.5 (3.1)	30	14.1 (2.9)	21	12.6 (3.3)
12 months	37	13.5 (3.6)	19	14.1 (4.1)	18	12.8 (2.9)
P-values: Evaluating the pattern of change						
Over time	<0.001*					
Comparing sMIGS v cMIGS over time, unadjusted	0.07					
Comparing sMIGS v cMIGS over time, adjusted[a]	<0.05*					

Notes: Mean intraocular pressure (IOP) at postoperative timepoints. Wald Tests were used to evaluate significant difference ($p < 0.05$) (*) between the pattern of change across timepoints, as well as comparatively between single MIGS (sMIGS) and combined MIGS (cMIGS). [a]Adjusted for baseline medications.

Table 3 Change in Medication Burden

Outcome: Medication Burden	Overall		sMIGS		cMIGS	
	N	Mean (SD)	N	Mean (SD)	N	Mean (SD)
Baseline	71	2.3 (1.9)	37	1.7 (1.9)	34	2.9 (1.6)
6 weeks	67	1.6 (1.6)	35	1.3 (1.6)	32	1.9 (1.4)
3 months	46	1.5 (1.5)	24	1.2 (1.7)	22	1.8 (1.3)
6 months	51	1.6 (1.6)	30	1.2 (1.5)	21	2.1 (1.6)
12 months	37	1.8 (1.7)	19	1.3 (1.5)	18	2.4 (1.7)
P-values: Evaluating the pattern of change						
Over time	0.03*					
Comparing sMIGS v cMIGS over time, unadjusted	0.02*					
Comparing sMIGS v cMIGS over time, adjusted[a]	0.75					

Notes: Medication number at postoperative timepoints. Wald Tests were used to evaluate significant difference ($p < 0.05$) (*) between the pattern of change across timepoints, as well as comparatively between single MIGS (sMIGS) and combined MIGS (cMIGS). [a]Adjusted for baseline medications.

In pairwise comparison of sMIGS and cMIGS, the reduction pattern in IOP approached a significant difference prior to adjustment ($p = 0.07$) and reached a significant difference favoring cMIGS after adjustment for baseline medications ($p < 0.05$). Prior to adjustment, the reduction patterns in medication burden were different between sMIGS and cMIGS, in favor of the former ($p = 0.02$). After adjustment for baseline medications, pairwise comparison of the GEEs for medication burden was not different ($p = 0.75$). Changes in IOP and medication burden stratified by individual procedure type are included in Supplemental Tables 2 and 3 respectively.

At 12 months, 47.5% (SE 13.9), 87.5% (5.3), and 64.7% (9.8) of patients achieved and maintained IOP ≤ 12 mmHg, 17 mmHg, or predetermined goal IOP, respectively, without additional medication or procedure (Figure 1). Using the SC12 criteria at 12 months, 31.9% (27.7) of the sMIGS group survived compared to 59.6% (15.5) of the cMIGS group, but the Kaplan–Meier curves were not statistically different ($p = 0.30$) (Figure 2). Survival by SC17 criteria was not different between sMIGS and cMIGS, with 87.5% (6.8) and 88.3% (7.4) survival, respectively, at 12 months ($p = 0.57$). Similarly, with a 12-month survival of 55.8% (17.3), survival in the sMIGS cohort under SCgoal criteria was comparable to that of the cMIGS cohort at 68.5% (12.9) ($p = 0.67$).

Procedural time averaged 40.61 minutes and was not different between sMIGS and cMIGS ($p = 0.56$) (Table 1). Subjects who underwent any of the combined cataract and MIGS surgeries experienced significant improvement in logMAR throughout GEE models across all timepoints ($p < 0.001$) (Supplemental Table 4). The pattern of improvement in logMAR was similar between sMIGS and cMIGS before and after adjustment for baseline medications ($p = 0.80$ and $p = 0.52$, respectively).

Postoperative Complications

Postoperative corneal edema resolved before 6 weeks, except in three cases where the finding persisted ≤6 months (Supplemental Table 5). Postoperative anterior chamber inflammation resolved before 6 months, except in one Phaco/ECP case, which persisted ≤12 months due to rebound iritis. Postoperative hyphema or microhyphema resolved 3 months ago. There were three cases of postoperative cystoid macular edema (CME) in patients who underwent either PEcK, ICE2, or Phaco/ECP.

For up to 60 months after Phaco/MIGS, additional procedural intervention was performed for 7 (9.9%) of 71 total eyes, including 4 eyes that were treated with cMIGS. Within 3 months, two PEcK subjects underwent further surgery for Xen Gel Stent insertion (Allergan Inc, Dublin, Ireland) in the operative eye, and one of these patients eventually required a trabeculectomy at 6 months after cMIGS. Additionally, one Phaco/Hydrus subject underwent a trabeculectomy in the

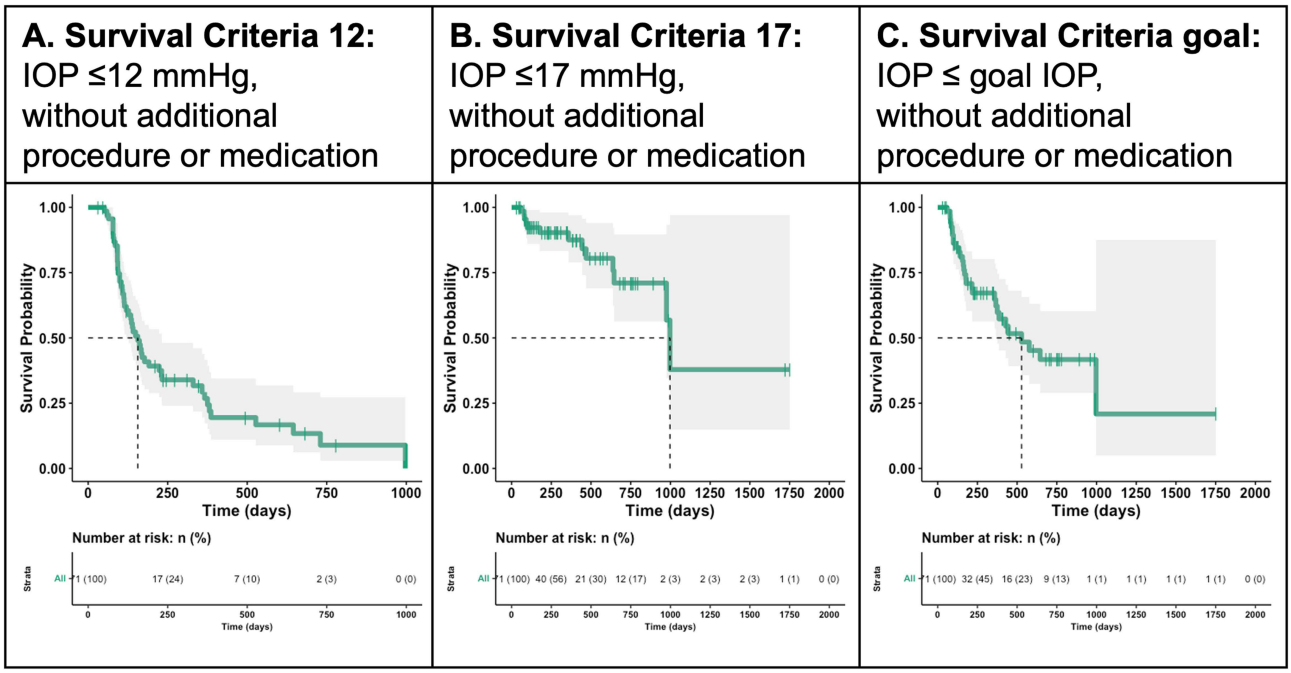

Figure 1 Survival Curves.
Notes: Kaplan-Meier Survival Estimates with Log rank tests of significance ($p < 0.05$) for Survival Criteria (**A**) 12, (**B**) 17, and (**C**) goal.
Abbreviation: IOP, intraocular pressure.

operative eye within 3 months. At 18 months postoperatively, an Ahmed Glaucoma Implant (New World Medical, CA, USA) was placed in the operative eye of a Phaco/KDB subject. Two PEcK subjects received a Baerveldt Glaucoma Implant (Medline Industries, IL, USA) in the operative eye at 24 and 36 months, respectively. Lastly, one subject received a Xen Gel Stent in the operative eye at 36 months postoperatively from Phaco/ECP.

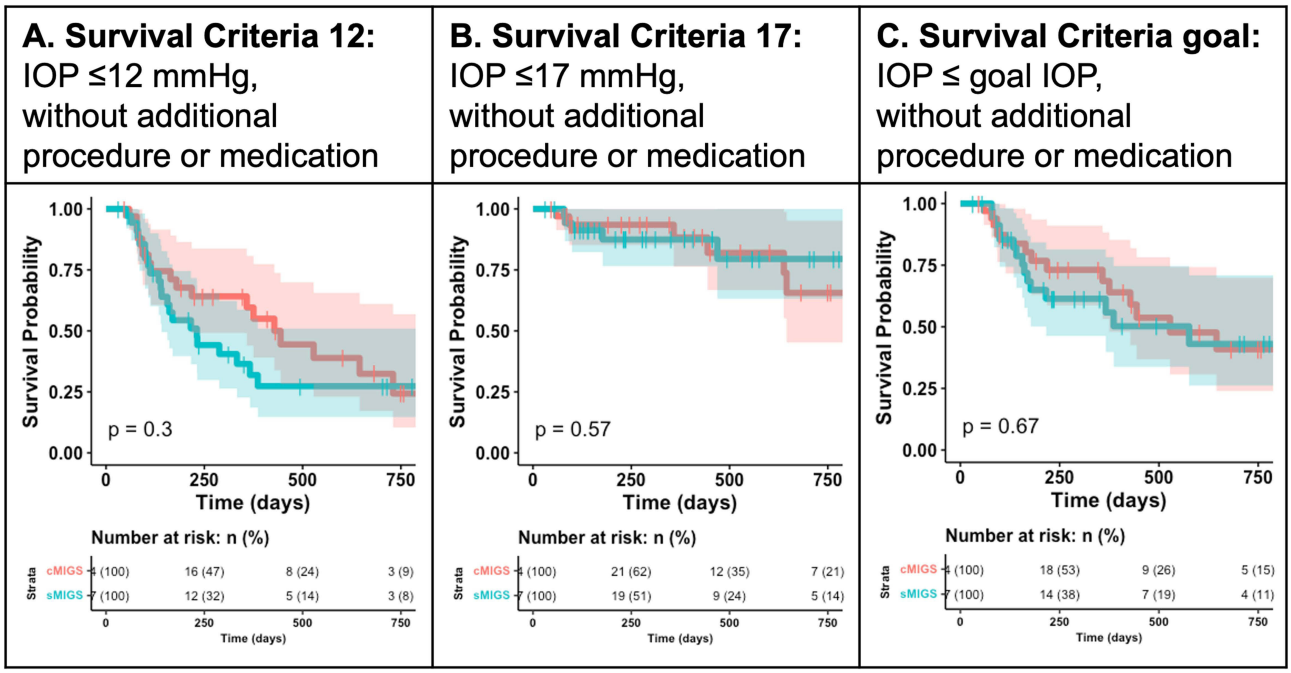

Figure 2 Survival Curves Stratified by Single or Combined MIGS.
Notes: Kaplan-Meier Survival Estimates with Log rank tests of significance ($p < 0.05$) for different Survival Criteria (**A**) 12, (**B**) 17, and (**C**) goal.
Abbreviation: IOP, intraocular pressure.

Discussion

This study demonstrates that patients with both severe glaucoma and cataract may benefit from reductions in IOP and in medication burden throughout 12 months following Phaco/MIGS. Further, we report the comparative efficacy of sMIGS and cMIGS for the first time in a population with severe glaucoma.

Performing Phaco/MIGS resulted in sustained patterns of reduction in IOP ($p < 0.001$) in patients with severe glaucoma for more than 12 months, with magnitudes comparable to those reported in the other studies of patients with predominantly mild or moderate glaucoma.[1,14–34] The postoperative IOP reduction was also associated with a simultaneous significant reduction in medication burden ($p = 0.03$).

Compared to 21.1% of the patients with preoperative IOP ≤ 12 mmHg, Phaco/MIGS had moderate efficacy at achieving and maintaining IOP ≤ 12 mmHg without additional medication or procedure, with a slight minority (47.5% (13.9)) surviving at 12 months. With cMIGS, a majority (59.6% (15.5)) achieved and maintained IOP ≤ 12 mmHg without additional medication or procedure at 12 months in comparison to 23.5% of the subjects with preoperative IOP ≤ 12 mmHg. Moreover, despite 29.6% of the patients with preoperative IOP ≤ predetermined goal IOP, the majority of patients achieved and maintained goal IOP at 12 months without additional medication or procedure, experiencing 64.7% (9.8) survival.

Importantly, Phaco/MIGS was safe in patients with severe glaucoma, in addition to improving visual acuity. Phaco/MIGS was associated with a low incidence of complications, including corneal edema, anterior chamber inflammation, hyphema, and CME. There was no postoperative hypotony, suprachoroidal hemorrhage, or endophthalmitis for up to 60 months. Although the suggested 12-month efficacy of Phaco/MIGS in patients with severe glaucoma is more modest than that reported following filtration surgery, it is notable that the reoperation rate of 9.9% for up to 60 months following Phaco/MIGS may be less that the 33% reported for filtration surgery failure within 36 months.[1,8,9] In terms of both efficacy and safety, Phaco/MIGS may serve as a stepping stone in severe glaucoma patients with visually significant cataract before proceeding with more invasive glaucoma surgery.

In a comparative analysis after adjusting for baseline medications, cMIGS conferred a greater pattern of IOP reduction than sMIGS ($p < 0.05$) with similarly reduced medication burden ($p = 0.75$) and without added procedural time ($p = 0.56$). All survival criteria are performed similarly between sMIGS and cMIGS. These results may suggest a possible additive or synergistic IOP-lowering effect from combining MIGS in a population with severe glaucoma for the first time.

This observational retrospective cohort study is limited by the lack of a standalone cataract surgery control group because proceeding with standalone cataract surgery would lack clinical equipoise in severe glaucoma patients with a majority of baseline IOP > IOP goal. Standalone cataract surgery is associated with a slight IOP reduction, and, although a lower reduction is expected with low or normal preoperative IOP, phacoemulsification confounds the overall benefit of sMIGS or cMIGS.[41] Further, there is selection bias from surgeon discretion for whether patients underwent sMIGS or cMIGS, as well as individual procedure types. Although we statistically adjusted for difference in baseline medications between sMIGS and cMIGS, the small sample size prevented direct comparisons between cMIGS and their constituent sMIGS. Because of this, the results of comparing sMIGS and cMIGS may be confounded by differences between individual procedures grouped in either cohort. It is also possible that additional unmeasured differences exist. A small sample size with attrition in all groups also limits the validity of this study. For this reason, analysis utilized Generalized Estimating Equations, which are often suggested as the preferred model type for interpreting population findings for continuous variables of repeated measurements without known distributions, with a small sample size, and to properly account for repeated outcome measurements.[37–39] The study may not be generalizable to all populations, particularly given that baseline mean IOP was within a normal range. Further, the main outcome measures of this study, including IOP, medication burden, visual acuity, and survival, are useful in assessing glaucoma management, but the study does not describe changes in retinal nerve fiber layers or in visual fields. The study adhered to the Guidelines on Design and Reporting of Glaucoma Surgical Trials from the World Glaucoma Association.[42]

In summary, performing phacoemulsification with MIGS in patients with cataract and severe glaucoma is associated with reductions in IOP and medication burden throughout 12 months, and there may be an additional IOP-lowering effect

from combining multiple MIGS. Phaco/MIGS should not be intended to replace filtration surgery. However, it could fill and possibly extend the gap between noninvasive treatment paradigms and filtration surgery, even in severe glaucoma, because Phaco/MIGS may reduce IOP with at least modest efficacy, may reduce the burden of medication compliance, and may be associated with lower risk of complications and shorter postsurgical convalescence time than filtration surgery. It will be vital to establish predictors of surgical efficacy from patient selection and individual characteristics of sMIGS or cMIGS in order to reduce and extend the low reoperation rates after Phaco/MIGS.

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Author Contributions

D.S.D and B.O. conceptualized this study. B.O., F.G.P., H.E.H, and H.F. collected the data. B.O. performed the statistical analysis with assistance from N.H. and J.T. B.O. drafted the article. D.S.D. contributed to the critical revision of the article. All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

D.S.D. is a consultant for AbbVie, New World Medical and BVI Medical and on the advisory board for Glaukos. No other conflicting relevant relationship exists for any author.

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