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BRIEF REPORT

Case Series of Combined iStent Implantation and Phacoemulsification in Eyes with Primary Angle Closure Disease: One-Year Outcomes

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ABSTRACT

Purpose: To evaluate the safety and efficacy of combined iStent® trabecular micro-bypass device (Glaukos, Laguna Hills, CA) and phacoemulsification in eyes with primary angle closure disease.

Methods: A two-center prospective interventional case series of consecutive patients with primary angle closure (PAC) or primary angle closure glaucoma (PACG) on at least one glaucoma medication, who underwent iStent implantation with cataract surgery. Postoperatively, patients were assessed on days 1 and 7, and months 1, 3, 6, and 12. The intraocular pressure (IOP), glaucoma medication use, visual acuity, and the presence of complications were assessed at each visit. Complete success was defined as IOP reduction of at least 20% without the use of glaucoma medications.

Results: Thirty-seven eyes with angle closure disease were included in this study. At 1-year, postoperative mean IOP (14.8 ± 3.94 mmHg) was significantly decreased compared with preoperative medicated (17.5 ± 3.82 mmHg, $p = 0.008$) and unmedicated (24.6 ± 3.41 mmHg, $p < 0.001$) IOP. Complete success was achieved in 89.2% of the eyes. The number of glaucoma medications decreased from 1.49 ± 0.77 to 0.14 ± 0.48 ($p < 0.001$). Preoperative medicated IOP was a risk factor for failure (hazard ratio 3.45, 95% confidence interval 1.52–7.85, $p = 0.003$), after adjustment for age, gender, and race. The most common postoperative complications were iStent occlusion with iris (27.0%) and hyphema (18.9%). There were

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no sight-threatening intraoperative or postoperative complications.
Conclusion: Combined iStent implantation with cataract surgery was effective in lowering the IOP and the number of glaucoma medications for at least 12 months, with a favorable safety profile.
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Keywords: Angle closure glaucoma; Case series; Minimally invasive surgery; Ophthalmology; Trabecular meshwork

INTRODUCTION

Primary angle closure glaucoma (PACG) is a leading cause of blindness in East Asian populations [1, 2]. The prevalence of PACG is between 1.0% and 1.4% in Asians aged 40 years and older [3, 4]. The primary angle closure disease spectrum ranges from primary angle closure suspect (PACS) to primary angle closure (PAC) and PACG [5]. When intraocular pressure (IOP) is elevated in association with a closed anterior chamber angle, the aims of treatment are to widen the anterior chamber angle and reduce the IOP [5]. Conventionally, laser peripheral iridotomy (LPI) is the first line of treatment for PAC and PACG [6]. In recent years, results from the EAGLE study [7] suggest that clear lens extraction is more effective in lowering the IOP and improving the quality of life compared with LPI [5]. However, in eyes with extended periods of iridotrabecular contact and raised IOP, trabecular damage may result in persistently raised IOP even after cataract removal has widened the anterior chamber angles [8, 9]. In this group of patients, randomized controlled trials by Tham et al. have shown that combined phacoemulsification and trabeculectomy results in a lower postoperative IOP and less requirement for topical glaucoma medications compared with phacoemulsification alone. However, trabeculectomy was associated with potentially sight-threatening complications, including hypotony and blebitis [9, 10]

In recent years, micro-invasive glaucoma surgery (MIGS) has emerged as an established treatment option for mild to moderate primary open angle glaucoma (POAG) [11]. Compared with conventional glaucoma surgery, MIGS devices are associated with a favorable risk profile and less tissue disruption [12]. The iStent trabecular micro-bypass stent (iStent®, Glaukos, Laguna Hills CA) is one of the first MIGS devices approved by the US Food and Drugs Administration [13–17]. It is a 1 mm by 0.33 mm stent made from surgical-grade, heparin-coated, non-ferromagnetic titanium, and drains aqueous from the anterior chamber to the Schlemm canal. The iStent trabecular micro-bypass stent has been shown to reduce the IOP to the mid-to-high teens, with a decrease in the number of topical hypotensive medications required and no serious adverse sequelae [18]. In addition to its effectiveness and safety, it has also been shown that iStent insertion is associated with cost savings when compared with bi-drug and tri-drug glaucoma therapy [19, 20].

iStent implantation is currently contraindicated for eyes with angle closure, and the outcomes of iStent implantation have not been reported in eyes with PAC or PACG. Hence, the aim of this study is to investigate the safety and efficacy of combined iStent trabecular micro-bypass stent implantation and phacoemulsification in eyes with PAC and PACG.

METHODS

This was a prospective interventional case series across two tertiary referral centers in Singapore (National University Hospital and Khoo Teck Puat General Hospital) of consecutive patients with PAC or PACG who underwent combined phacoemulsification with iStent trabecular micro-bypass stent implantation. All procedures performed were in accordance with the respective ethics committees of both hospitals and adhered to the tenets of the Declaration of Helsinki of 1964, and its later amendments. (National Healthcare Group Domain Specific Review Board (NHG DSRB), approval number 2017/00219.) Informed consent was obtained from all patients prior to surgery.

Study Subjects

Subjects with PAC or PACG who required at least one glaucoma medication and who were phakic in the same eye were included in this study. PAC was defined as eyes in which the posterior trabecular meshwork was not visible for at least 180° on gonioscopy in the primary position, elevated IOP (> 21 mmHg) with or without peripheral anterior synechiae (PAS) in the absence of glaucomatous optic neuropathy or visual field loss [21]. Primary angle closure glaucoma was defined as eyes with PAC and glaucomatous optic neuropathy as defined by Foster et al. [22]. Cases of newly diagnosed PAC or PACG were offered the opportunity to be included in the study and undergo combined phacoemulsification, with iStent implant or to undergo the standard of care, laser peripheral iridotomy, or phacoemulsification alone. Subjects recruited for the study were provided the first iStent free-of-charge, and were offered the opportunity to have a second iStent implanted during the surgery at their own expense. The decision to have either one or two iStents was based on the subject's willingness to pay for the second iStent. Exclusion criteria included advanced PACG (as defined by cup-disk ratio $\geq$ 0.9 and/or a visual field defect within central 10° of fixation) [23], greater than 180° of PAS, PAS in the nasal quadrant (the target site of iStent implantation), a history of acute primary angle closure, other forms of glaucoma (including uveitic, neovascular, traumatic glaucoma, or glaucoma secondary to raised episcleral venous pressure) and any corneal, choroidal, retinal, orbital disease which may interfere with cataract extraction or iStent implantation.

Surgical Technique

Phacoemulsification and iStent implantation were performed by one of three surgeons (CS, TS, or JC) all of whom have performed more than 100 iStent surgeries. All surgeries were performed under topical anesthesia or a peribulbar block. Phacoemulsification was performed via a standard clear corneal incision with acrylic intraocular lens implantation from a temporal approach. The pre-loaded single-use iStent injector (Glaukos, Laguna Hills, CA, GTS100i) was advanced through the temporal incision across the anterior chamber and implanted into the nasal Schlemm canal, under direct visualization of the angle with an intraoperative gonioscopy lens (Ocular Hill Open Access Surgical Gonioscopy [Left-Hand], Ocular Instruments, Bellevue, WA). If a second iStent was to be implanted, this was inserted at the nasal quadrant, targeted at a location corresponding to blood reflux in the Schlemm canal. The corneal incisions were hydrated and intracameral cefazolin was administered at the end of the surgery.

Postoperatively, all glaucoma medications were discontinued, and patients were prescribed Tobradex (tobramycin 0.3% with dexamethasone 0.1%) or Chlorodex (chloramphenicol 0.5% with dexamethasone 0.1%) eyedrops on a 3-hourly basis for a week. From the second week onwards, the medication frequency was reduced to QDS and further tapered over a period of 4 to 6 weeks according to the severity of intraocular inflammation.

Study Measures

Participants had a complete ophthalmic examination preoperatively and postoperatively on day 1, week 1, and months 1, 3, 6, and 12. This included assessment of the best corrected visual acuity (VA) and a detailed slit lamp examination of the anterior and posterior segments. Gonioscopy was performed in a darkened room with a 4-mirror goniolens (Volk Optical Inc, Mentor, Ohio, USA), using a narrow beam of light with care taken to avoid directing the light within the pupil [24]. The mean deviation was recorded from the patients' visual field performed at the time of recruitment (Swedish Interactive Threshold Algorithm Standard 24–2 algorithm, Humphrey Visual Field Analyzer II, Carl Zeiss Meditec, Inc., Dublin, California, USA). Anterior chamber depth (ACD) and axial length (AL) were measured using the IOLMaster 700 (Carl Zeiss Meditec, Inc., Dublin, California, USA). Goldmann applanation tonometry was

used to measure IOP, taken as the mean of two measurements. If the two IOP measurements differed by more than 2 mmHg, a third IOP measurement was performed and the median of these three readings was recorded. Study subjects were instructed to stop all medications for 4 weeks and return for measurement of the unmedicated IOP at a baseline visit prior to the surgery.

The primary outcome measure was IOP reduction at 12 months compared to baseline. Complete success was defined as at least 20% IOP reduction to an IOP of at most 18 mmHg without the use of glaucoma medications. Qualified success was defined as at least 20% IOP reduction to an IOP of at most 18 mmHg with or without the use of glaucoma medications. Secondary outcome measures included the reduction in glaucoma medications and the occurrence of complications during or after the surgery.

Statistical Analysis

Statistical analyses were performed using SPSS v20.0 (IBM Corp., Armonk, NY, USA) and STATA v15.0 (StataCorp., College Station, TX, USA). Descriptive statistics were used to describe baseline characteristics for the study patients. Differences between pre- and postoperative values were analyzed using the Wilcoxon signed rank test. Kaplan–Meier analysis was used to describe cumulative probabilities of survival at 12 months in our study cohort. Cox regression analysis, adjusted with a clustered (robust) standard errors method for the effect of bilateral eyes included in the study, was used to identify possible factors associated with failure and iStent occlusion (complete or partial occlusion), with significant results further adjusted for age, gender, and ethnicity. Statistical significance was set at alpha 0.05 (two-sided).

RESULTS

The demographic characteristics of the study subjects are shown in Table 1. A total of 37 eyes of 31 patients were included in this study and followed up for 12 months. Two iStents were

Table 1 Baseline characteristics of study subjects

	Number (%) or mean ±SD
Age	68.70 ± 6.39
Gender	
Male	16 (43.2%)
Female	21 (56.8%)
Ethnicity	
Chinese	33 (89.2%)
Malay	1 (2.7%)
Indian	3 (8.1%)
Laterality	
Right	15 (40.5%)
Left	22 (59.5%)
Laser peripheral iridotomy	
Yes	29 (78.4%)
No	8 (21.6%)
Preoperative glaucoma medications	
0	1 (2.7%)
1	22 (59.5%)
2	9 (24.3%)
3	5 (13.5%)
Diagnosis	
Primary angle closure (PAC)	19 (51.3%)
Primary angle closure glaucoma (PACG)	18 (48.6%)
Preoperative VA (logMAR)	0.32 ± 0.22
Preoperative medicated IOP (mmHg)	17.50 ± 3.82
Preoperative unmedicated IOP (mmHg)	24.60 ± 3.40
Preoperative medications	1.49 ± 0.77
HVF mean deviation	− 6.27 ± 2.60
Axial length (mm)	22.90 ± 0.72

Table 1 continued

	Number (%) or mean ±SD
Anterior chamber depth (mm)	2.60 ± 0.32

VA visual acuity, *IOP* intraocular pressure, *HVF* Humphrey visual field, *logMAR* logarithmic minimum angle of resolution, *SD* standard deviation

implanted in 16 eyes, and one iStent was implanted in 21 eyes.

The postoperative IOP and number of glaucoma medications are shown in Table 2. Mean IOP at 12 months was 14.8 ± 3.9 mmHg ($p = 0.008$) with patients using a mean of 0.14 ± 0.48 ($p < 0.001$) IOP-lowering medications. There is a significant improvement in the best corrected VA at month 12 compared with the preoperative VA (logMAR VA 0.10 ± 0.10 vs 0.32 ± 0.22, $p < 0.001$). The 12-month cumulative Kaplan–Meier survival probability was 89.2% for complete success and 94.6% for qualified success (Figs. 1, 2). The IOP trend across the 12-month visits is shown in Fig. 3. Univariate Cox regression modeling identified preoperative medicated IOP to be significantly associated with failure to achieve complete success (Table 3). For every 1-mmHg increase in IOP, the risk of failure was increased by 1.55 times (95% confidence interval [CI] 1.19–2.02, $p = 0.001$). After adjustment for age, gender, and race, preoperative IOP remained

Table 2 Postoperative outcomes

	Preoperative (mean ± SD)	Postoperative (mean ± SD)	*p* value
VA (logMAR)	0.32 ± 0.22	0.10 ± 0.10	< 0.001
IOP (mmHg)			
Medicated	17.50 ± 3.82	14.80 ± 3.94	0.008
Unmedicated	24.60 ± 3.40		< 0.001
Medications used	1.49 ± 0.77	0.14 ± 0.48	< 0.001

VA visual acuity, *IOP* intraocular pressure, *logMAR* logarithmic minimum angle of resolution, *SD* standard deviation

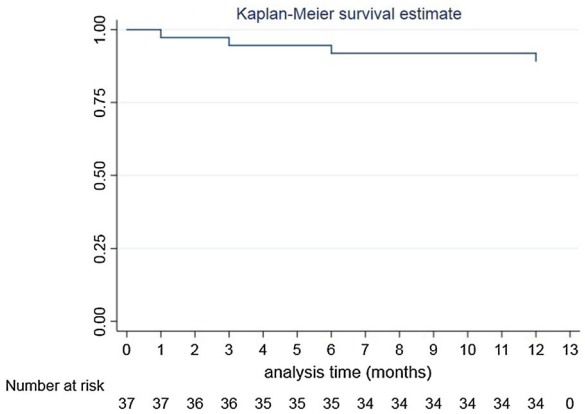

Fig. 1 Kaplan–Meier survival curve for complete success

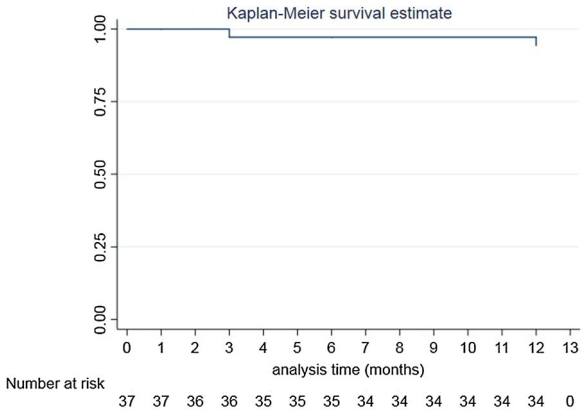

Fig. 2 Kaplan–Meier survival curve for qualified success

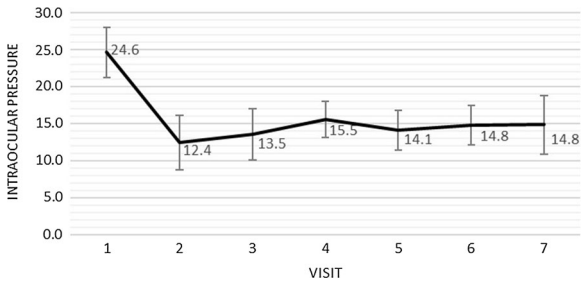

Fig. 3 Graph showing trend of IOP against time

significantly associated ($p = 0.003$) with failure, with 3.45 (95% CI 1.52–7.85) times increased risk of failure for every 1-mmHg rise in IOP (Table 4).

The complications associated with combined phacoemulsification and iStent implantation are shown in Table 5. All complications were

Table 3 Univariate cox proportional hazard for failure to achieve complete success at 12 months

Risk factor	Univariate hazard ratio	95% CI for hazard ratio		*p* value
		Lower	Upper	
Age	0.38	0.04	3.36	0.616
Gender—Female	0.71	0.10	5.10	0.733
Race—Chinese	0.38	0.05	3.15	0.385
Diagnosis—PAC	0.89	0.13	6.19	0.908
Preoperative medicated IOP	1.55	1.19	2.02	0.001
Preoperative no. of medications	3.62	0.96	13.61	0.057
Preoperative unmedicated IOP	1.11	0.95	1.31	0.190
Preoperative VA	0.02	0.00	14.47	0.249
PAS degrees	1.00	0.99	1.01	0.827
MD	1.02	0.83	1.26	0.826
ACD	6.45	0.66	62.73	0.108
AL	1.87	0.94	3.75	0.076
Surgeon (reference = JC)	1.41	0.20	10.17	0.734
Number of iStents inserted	1.25	0.18	8.93	0.822
iStent occlusion	3.22	0.47	21.90	0.231

CI confidence interval, *PAC* primary angle closure, *IOP* intraocular pressure, *VA* visual acuity, *PAS* peripheral anterior synechiae, *MD* mean deviation, *ACD* anterior chamber depth, *AL* axial length

managed conservatively without requiring a second surgery and no sight-threatening complications occurred. The most common postoperative complications were iStent occlusion with iris (27.0%) and hyphema (18.9%).

Amongst the 10 eyes which had an iStent occlusion, eight eyes had a single iStent implanted and two eyes had two iStents implanted. The occlusion occurred within the first 2 months after the surgery in seven eyes and glaucoma medications were subsequently required in 3 of the 10 eyes (5.6% of all cases). Five of the eight eyes with a single iStent in situ was fully occluded with iris (Fig. 4). The remaining five eyes contained partially occluded iStents.

Of the three eyes requiring medication, two had a single completely occluded iStent in situ and required two glaucoma medications to control their IOP, as compared to their three glaucoma medications required preoperatively. The remaining eye required one additional glaucoma medication with a partially occluded and patent iStent in situ. Three eyes had single fully occluded iStents in situ, but did not require any glaucoma medications, whilst one eye with two patent iStents in situ still required one additional glaucoma medication for IOP control.

Univariate Cox regression modeling identified increased preoperative medicated IOP and increased ACD to be significantly associated with iStent occlusion ($p = 0.006$ and $p = 0.018$, respectively) (Table 6). After adjustment for age, gender, and race, the risk of iStent occlusion is increased by 1.33 times (95% CI 1.06–1.67) for every 1-mmHg rise in IOP ($p = 0.009$), and by 6.21 times (95% CI 1.15–33.47) for every 1-mm increase in ACD ($p = 0.013$) (Table 7).

Table 4 Multivariate Cox proportional hazard for failure to achieve complete success at 12 months

Variables	Multivariate hazard ratio	95% CI for hazard ratio		*p* value
		Lower	Upper	
Age	0.95	0.85	1.06	0.349
Gender (reference = female)	0.65	0.10	4.29	0.657
Race (reference = Chinese)	0.25	0.02	2.96	0.269
Preoperative medicated IOP	3.45	1.52	7.85	0.003

95% CI 95% confidence interval, *IOP* intraocular pressure

Table 5 Complications

	Number of eyes
Intraoperative	
Iridodialysis	1 (2.7%)[a]
Lens damage	0
Retrobulbar hemorrhage	0
Suprachoroidal hemorrhage	0
Postoperative	
Hyphema	7 (18.9%)
Occlusion of iStent with iris	10 (27.0%)
Raised IOP	1 (2.7%)
Iris atrophy	2 (5.4%)
Cornea edema	1 (2.7%)[b]
Shallow AC	0
Hypotony	0
Endophthalmitis	0

[a] Extent of iridodialysis less than one clock hour
[b] Cornea edema resolved by postoperative week 1

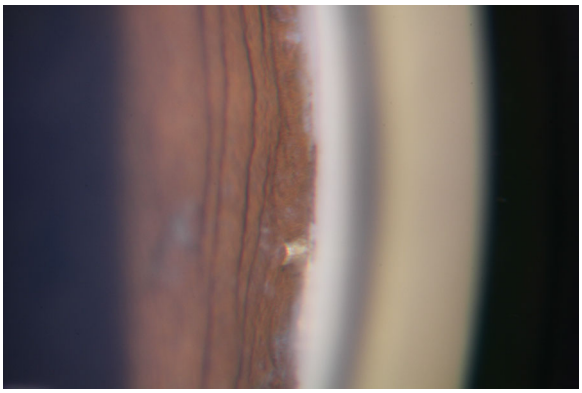

Fig. 4 Slit lamp gonioscopy photograph showing a completely occluded iStent

DISCUSSION

Our exploratory study has shown that combined phacoemulsification with iStent trabecular micro-bypass stent insertion was effective in lowering the IOP in patients with primary angle closure disease, with low complication rates. A total of 89.2% of patients were medication-free at 1 year, with higher preoperative medicated IOP found to be associated with failure to achieve complete success. The most common postoperative complication was iStent occlusion with iris, which occurred in approximately one-quarter of angle closure eyes.

We provide novel data on the outcomes of combined phacoemulsification and iStent implantation in eyes with primary angle closure disease. In our study, mean IOP decreased by 15.4% compared with preoperative medicated IOP, and 39.8% compared with preoperative unmedicated IOP. This was associated with a reduction in the number of glaucoma medications required by 90.6% (1.4 ± 0.7 medications) with 89.2% of eyes being medication-free at 1 year. These results are comparable to that of combined phacoemulsification and iStent implantation in POAG eyes, with the reduction in IOP reported to be 16–33% and the reduction in medications reported to be 0.5–2.0 in previous studies [14–16, 25]. In eyes with angle closure, cataract surgery alone has also been shown

Table 6 Univariate Cox proportional hazard for iStent occlusion at 12 months

Risk factor	Univariate hazard ratio	95% CI for hazard ratio		*p* value
		Lower	Upper	
Age	0.96	0.89	1.04	0.315
Gender—Female	1.08	0.30	3.92	0.910
Race—Chinese	7.23e14	2.06e14	2.53e15	< 0.000
Diagnosis—PAC	0.56	0.15	2.19	0.407
Preoperative medicated IOP	1.28	1.07	1.53	0.006
Preoperative no. of medications	1.92	0.73	5.09	0.189
Unmedicated IOP	1.08	0.94	1.25	0.258
Preoperative VA	1.34	0.10	18.36	0.825
PAS degrees	1.00	0.99	1.00	0.530
MD	1.00	0.87	1.15	0.994
ACD	7.13	1.40	36.43	0.018
AL	1.42	0.78	2.61	0.250
Surgeon (reference = JC)	1.49	0.41	5.45	0.545
Number of iStents inserted	0.26	0.05	1.29	0.099

CI confidence interval, *PAC* primary angle closure, *IOP* intraocular pressure, *VA* visual acuity, *PAS* peripheral anterior synechiae, *MD* mean deviation, *ACD* anterior chamber depth, *AL* axial length

to reduce IOP [7]. However, randomized controlled trials comparing cataract surgery alone with combined cataract surgery and trabeculectomy showed that the combined procedure was more effective at reducing the number of medications, at the expense of a higher rate of complications [9, 10]. This is likely because prolonged iridotrabecular contact in some angle closure eyes results in trabecular damage leading to elevated IOP even when the angles are open after cataract surgery. iStent implantation in such eyes would allow aqueous flow to bypass the increased trabecular resistance, which may explain the high proportion of eyes that are medication-free in our study. Our prospective study agrees with that of Chansangpetch et al. which retrospectively showed similar iStent efficacy rates in eyes with angle closure disease undergoing combined iStent and phacoemulsification compared to eyes undergoing phacoemulsification alone, but with significantly reduced number of medications [26].

Higher preoperative medicated IOP was associated with failure to achieve complete success in our study. The dimensions and flow rate of the iStent implant could act as a limiting factor for the outflow into collector channels of the trabecular meshwork [27], and hence eyes with higher preoperative IOP are also more likely to have higher postoperative IOP and are more likely to require glaucoma medications after the surgery. It is also possible that aqueous flow in the collector channels and aqueous veins is impaired in angle closure eyes with higher preoperative IOP, hence bypassing the trabecular meshwork in such eyes may not be as effective in lowering the IOP, as seen in one of our cases requiring glaucoma medications despite two patent iStents in situ. Advancements in anterior segment optical coherence tomography angiography and confocal microscopy techniques may verify this hypothesis in the future. These results suggest that the effectiveness of combined iStent implantation and

Table 7 Multivariate Cox proportional hazard for iStent occlusion at 12 months

Variables	Multivariate hazard ratio	95% CI for hazard ratio		*P* value
		Lower	Upper	
Age	0.97	0.89	1.06	0.506
Gender (reference = female)	1.33	0.32	5.52	0.694
Race (reference = Chinese)	4.86e15	–	–	–
Preoperative medicated IOP	1.33	1.06	1.67	0.009
ACD	6.21	1.15	33.47	0.013

95% CI 95% confidence interval, *IOP* intraocular pressure, *ACD* anterior chamber depth

phacoemulsification may be limited in patients with medically uncontrolled glaucoma and markedly raised baseline IOP.

We provide novel data that combined phacoemulsification and iStent implantation had a good safety profile in angle closure eyes, with no sight-threatening complications reported. The most common postoperative complication was occlusion of the iStent by iris, which occurred in 27.0% of the study subjects. This was higher than the reported rates of iStent occlusion in eyes with POAG, which ranged from 4% to 18% [25]. Surprisingly, iStent occlusion was not associated with failure in our study, possibly because our study was not adequately powered to detect such an association. A complete iStent occlusion did not necessarily result in a raised IOP and a requirement for glaucoma medications. This could be because phacoemulsification alone sufficiently lowered the IOP in these eyes.

Our data indicate that a higher preoperative medicated IOP and an increased preoperative ACD were significantly associated with iStent occlusion. In eyes with angle closure mechanisms associated with a deeper ACD, e.g., plateau iris and a thick peripheral iris roll [28], the anterior chamber angle would still be crowded after cataract surgery, predisposing such eyes to iStent occlusion by the peripheral iris. Another common postoperative complication after combined phacoemulsification and iStent implantation in angle closure eyes was hyphema, which occurred in 18.9% of our study subjects. All subjects were managed conservatively, and the hyphema resolved by postoperative week 1. Hyphema is also commonly reported following iStent implantation in POAG eyes, with the reported incidence varying greatly from 2.3% to 70% [18], and has been associated with blood reflux from the aqueous veins.

The strengths of our study include the two-center design and the complete data set, with no patients being lost to follow-up. However, our study had several limitations. First, the 1-year follow-up duration precluded an analysis of visual field progression. Second, there was inadequate statistical power for subgroup analyses. Third, it was not possible to determine the additional effect of iStent implantation in lowering the IOP compared with phacoemulsification alone, and a randomized study, in tandem with a cost–benefit analysis, comparing phacoemulsification alone versus combined procedure is warranted. Lastly, we did not include information on the type of glaucoma medications used by participants within our study, though this is unlikely to affect the success of combined phacoemulsification and iStent implantation as this is a bleb-less conjunctiva-sparing procedure.

CONCLUSION

This exploratory study showed that combined phacoemulsification and iStent implantation was effective in lowering the IOP and the number of glaucoma medications for at least 1 year. Almost 90% of study subjects were medication-free at 1 year, and higher preoperative medicated IOP was associated with failure to achieve complete success. Although combined phacoemulsification and iStent implantation had a favorable safety profile in our study, iStent

occlusion by iris occurred in approximately one-quarter of angle closure eyes. A randomized controlled study comparing phacoemulsification alone with the combined procedure is required to determine the efficacy of iStent implantation in angle closure eyes.

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

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Compliance with Ethics Guidelines. All procedures performed were in accordance with the respective ethics committees of both hospitals and adhered to the tenets of the Declaration of Helsinki of 1964, and its later amendments. This study was approved by the National Healthcare Group Domain Specific Review Board (NHG DSRB), approval number 2017/00219. Informed consent was obtained from all patients prior to surgery.

Data Availability. The data sets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

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