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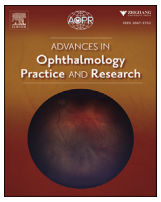

Full Length Article

Real-world assessment of second-generation trabecular micro-bypass stents in open-angle glaucoma patients

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ABSTRACT

Background: To assess the safety and efficacy of iStent inject placement in individuals with glaucoma with open angles in real world clinical settings.
Methods: A review was conducted on the medical records of individuals who received iStent inject implants starting from March 2018. The analysis focused on reductions in intraocular pressure (IOP) and glaucoma medication usage. Safety assessments encompassed intraoperative and postoperative issues, additional surgeries, and improvements in best-corrected visual acuity (BCVA).
Results: Analysis of 55 eyes of 48 patients that underwent iStent implantation revealed a mean age of 77 years (range: 51–97). The initial average intraocular pressure (IOP) in these eyes was 20.2 ± 6.4 mm Hg. Following surgery, IOP decreased by ≥ 20% compared to preoperative levels in 21 eyes (43.8%) over the 12-month follow-up period. Notably, there was a significant reduction in medication usage by the 12-month mark ($P < 0.0042$). Among the evaluated eyes, 9 exhibited a response to steroids, 3 had stents that were improperly positioned, 5 had stents that were over implanted, and 1 eye experienced an episode of iris prolapse.
Conclusions: The findings from the 12-month follow-up of iStent inject implants in standard clinical settings demonstrate a notable decrease in both intraocular pressure (IOP) and medication usage in eyes with concurrent open-angle glaucoma.

1. Introduction

Glaucoma, a progressive vision-threatening condition encompassing various optic neuropathies, poses a significant global health burden. Among its forms, primary open-angle glaucoma (POAG) stands out as the most prevalent, projected to impact over eighty million individuals by 2020 and remains a leading cause of blindness in developing nations.[1] The irreversible optic nerve damage associated with glaucoma underscores the critical need for treatments aimed at preserving optic nerve structure and visual function.[2] Central to this goal is the reduction of intraocular pressure (IOP), the primary modifiable risk factor linked to glaucoma progression and visual field loss. Notably, studies like the Early Manifest Glaucoma Trial (EMGT) have highlighted the strong correlation between decreased IOP and reduced risk of glaucoma progression.[3]

While POAG, along with other forms of glaucoma like normal-tension glaucoma (NTG), pseudoexfoliation glaucoma (PXG), and ocular hypertension (OHT), often presents insidiously without symptoms, elevated IOP due to impaired aqueous humor outflow remains a key feature. Current treatment modalities primarily focus on IOP reduction through medications and laser procedures, yet challenges such as compliance issues and side effects persist.[4] Factors contributing to glaucoma's onset are multifaceted, including age, diabetes, myopia, family history, and ethnicity.[5] Other factors like low cerebrospinal fluid pressure, poor ocular blood perfusion and genetic predisposition also play a significant role in the disease aetiology of variants like NTG.[5,6] Traditionally, initial management involves antiglaucoma medications; however, when target IOP levels are not met or disease progression continues despite maximal therapy, surgical intervention becomes necessary.[7] Unfortunately, the more invasive surgical techniques like trabeculectomy and tube surgeries are associated with sight-threatening complications that may result in a blebitis, haemorrhage, hyphema, hypotony, endophthalmitis, inflammation, loss of vision or repeat surgery.[8] Micro Invasive Glaucoma Surgery (MIGS) has emerged as a less invasive alternative to traditional surgeries like trabeculectomy, offering promising outcomes in lowering IOP. Trabecular bypass micro stents represent a key advancement in MIGS, providing a novel route for aqueous humor drainage and

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demonstrating significant reductions in both IOP and medication burden.[9,10] Randomized, controlled studies have shown significant reductions in both IOP and medication load post-implantation of one or more micro stents in conjunction with cataract surgery, beyond the reductions achieved with cataract surgery alone.[4,11,12]

This retrospective study focuses on evaluating the outcomes of implanting 2 s-generation trabecular micro-bypass stents in diverse glaucoma cases within real-world settings. By including patients often excluded from clinical trials due to specific criteria, such as those with pseudoexfoliation glaucoma or advanced disease, this research aims to provide valuable insights into the practical application of these innovative devices.

2. Methods

2.1. Ethical approval

All procedures were conducted following approval from the Institutional Review Board of Lancashire Teaching Hospital, Preston, in accordance with the principles outlined in the 1964 Helsinki declaration and its subsequent revisions or equivalent ethical guidelines. The study was registered with the research and development department of the institution. As the data collection was retrospective, it focused on patients already treated within the surgeon's clinical practice, obviating the need for formal clinical trial registration. Patient details were meticulously recorded to prevent duplication, ensuring anonymity and confidentiality were rigorously upheld.

Each case record was assigned a random number for study purposes, with a separate secure, password-protected system storing the key linking these numbers to patient names. Subjects' rights and welfare were safeguarded by presenting aggregated, anonymized data derived solely from medical chart reviews. Data extraction was directly from EVOLVE without the use of paper forms, with de-identified information securely stored in a password-protected database on a restricted network drive.

2.2. Methods

This study retrospectively examined the clinical records of patients who underwent iStent inject implantation consecutively between January 2017 and December 2018. Preoperative criteria included open-angle glaucoma with visible trabecular meshwork on gonioscopy, encompassing POAG, PXG, Pigmentary glaucoma (PG), NTG, mixed mechanism glaucoma, and OHT. Patients with glaucoma progression despite maximal antiglaucoma medications and poor ocular surface were included, irrespective of disease severity.

Exclusion criteria comprised eyes with active inflammation, corneal opacities hindering gonioscopy assessment, primary angle-closure glaucoma (PACG) and suspects, neovascular glaucoma, synechial angle closure, and elevated episcleral venous pressure. Pregnant women, individuals under 18 years old, and those with congenital glaucoma were not enrolled. Patients lost to follow-up or with significant ocular comorbidities were also excluded.

The iStent inject procedure is routinely performed at the ophthalmology department of Royal Preston Hospital. To ensure statistical significance, a large sample size was maintained, aiming for approximately 120 cases annually with a 10% attrition rate considered. The sample size was estimated at 200–220 cases to account for potential losses to follow-up post-surgery. However, the sample size in our study was smaller after taking inclusion and exclusion criteria into consideration. Patients with a followup of less than six months were also excluded.

Data collection utilized a structured proforma overseen by the principal investigator, which was piloted to identify and rectify any study-related errors. File numbers of patients undergoing the iStent inject procedure were retrieved from surgical records and electronically documented using EVOLVE software. Preoperative data encompassed demographics, best corrected visual acuity (BCVA), IOP, central corneal thickness (CCT), and preoperative medication details.

Postoperative information included IOP and medication burden at various intervals up to twelve months. Safety parameters recorded comprised postoperative BCVA, surgical complications, additional interventions. Patients had a minimum follow-up of six months post-operatively to enhance result validity. All adverse events and complications were meticulously documented, with 'Serious' adverse events meeting specific criteria such as life-threatening nature or requiring hospitalization.

A successful outcome post Istent was defined as $\geq$ 20% reduction in intraocular pressure (IOP) at 12 months without additional glaucoma surgery or medications, in line with the World Glaucoma Association's (WGA) recommendations.

2.3. iStent inject design and surgical procedure

The iStent, developed by Glaukos Inc., is a first-generation trabecular bypass device that connects the anterior chamber to Schlemm's canal. This device, approved by CE-mark and FDA, can be used independently or in conjunction with cataract surgery in Europe. It measures 1 mm $\times$ 0.3 mm, is constructed from heparin-coated, non-magnetic titanium, and comes pre-loaded in an inserter. The iStent inject, also known as the GTS-400 iStent inject, represents a second-generation model made of heparin-coated titanium with dimensions of 360 μm length and 230 μm diameter. Significantly smaller than its predecessor, the iStent inject is the smallest approved implantable medical device designed to reduce IOP effectively and safely.

Featuring a simplified learning curve due to its updated design compared to the original iStent, which had a snorkel structure, the G2-M-IS injector system allows for simultaneous implantation of two stents during a single procedure. Surgeons use this system to insert the stents into Schlemm's canal via a stainless-steel insertion tube by pressing a button on the injector. Each iStent inject stent is positioned in the nasal trabecular meshwork and Schlemm's canal at specific angles to facilitate multidirectional aqueous outflow through two fenestrations. The procedure can be performed through a temporal phacoemulsification incision or a temporal clear corneal incision as a standalone operation.

During surgery, patients are positioned supine with their head turned 35° counterclockwise for optimal visualization of the nasal angle using a direct gonioscope rotated 135° at the microscope eyepiece. Postoperatively, patients follow a standard regimen involving antibiotic (chloramphenicol 0.5%) eye drops for one week and anti-inflammatory (dexamethasone 1%) eye drops four times daily for four weeks with a gradual taper over one month. Glaucoma medications are typically continued preoperatively and may be adjusted postoperatively based on achieving target IOP levels at the surgeon's discretion.

The positioning of the iStent inject is evaluated gonioscopically both during and after surgery at each clinical visit.

2.4. Statistics

In the study, descriptive statistics were employed to analyze the data. This involved determining means, frequencies, and proportions of the variables, with results presented through appropriate graphs, tables, and charts. The comparison of preoperative and postoperative IOP at different time points was conducted independently, along with assessing the effectiveness of the procedure by comparing preoperative IOP with IOP at 12 months. Additionally, preoperative and postoperative medication usage was compared. Categorical and numerical variables were analyzed using the Chi-square test and Student's *t*-test, respectively. Statistical significance was defined as a p-value below 0.05. Data analysis was performed using SPSS statistical software (IBM Corp., Armonk, NY, USA).

3. Results

A total of 55 consecutive eyes of 48 patients who underwent iStent inject with a minimum of six months of follow-up data were included in the study. The mean age at the time of surgery was 77 years (SD = 10.4; range 51–97). The patient population predominantly consisted of individuals with POAG, PXG, and PD, all exhibiting an open-angle configuration at the stent implantation site. Among the eyes, 98.2% (n = 54) underwent simultaneous phacoemulsification and iStent inject implantation, while only one phakic eye received solely iStent inject implantation. Additionally, 7.3% (n = 4) of eyes were diagnosed with PD and 3.6% (n = 2) were diagnosed with PXG. Complete preoperative parameters and demographics are detailed in Table 1.

The mean IOP decreased significantly from 20.2 ± 6.4 mmHg to 16.3 ± 4.77 mmHg in iStent eyes ($p < 0.0001$) at the 12-month postoperative mark (Fig. 1). A mean percentage reduction of IOP by 14.1% was observed at the 12-month follow-up compared to baseline. There was no statistically significant difference noted in IOP between post-iStent inject measurements at 1 month and 12 months ($p = 0.0995$). Notably, twenty-one eyes (43.8%) achieved a reduction of 20% or more in IOP at the 12-month follow-up period. The mean changes in IOP over various intervals - 1 week, 1 month, 3 months, 6 months, 9 months, and 12 months - are presented in Fig. 2.

The average medication burden decreased from 2.4 ± 0.91 topical anti-glaucoma medications preoperatively to 1.79 ± 1.18 medications at 12 months in iStent inject eyes, reflecting a 25.0% reduction ($P < 0.0042$) (Fig. 3). At the 12-month mark, twenty-three eyes (47%) showed a decrease in medication compared to preoperative usage, while 41.6% (n = 20) had no change in medication postoperatively. A rise in medication requirement was observed in 10 % (n = 5) of eyes. The proportion of eyes using 2 or more medications decreased from 78.1% (n = 45) preoperatively to 56.2% (n = 29) postoperatively after one year. Notably, eight eyes (14.5%) did not require any medication to achieve the target IOP at the 12-month follow-up. The alterations in medication usage across different follow-up periods are outlined in Fig. 4.

During surgery, 3 eyes (5.5%) experienced malpositioning of iStent inject implants, while 5 eyes (9.1%) had implants placed too deeply. In the postoperative phase, 9 eyes (16.4%) exhibited elevated IOP and were identified as steroid responders, representing the most common complication post-surgery. These cases were managed with eye drops and did not lead to any further issues or recurrence. Additionally, two eyes (3.6%) developed retinal vein occlusion postoperatively, resulting in reduced vision to hand motion at the one-year follow-up. One eye showed persistent corneal folds at one month, which resolved with an extended steroid regimen.

No adverse events were reported in the iStent inject eyes. There were no instances of persistent intraocular inflammation or peripheral anterior synechiae (PAS) in either group. None of the eyes underwent a secondary glaucoma procedure during the follow-up period. Table 2 provides a summary of surgical complications associated with iStent inject implants.

Table 1
Patient Demographics and Preoperative characteristics.

		N (55)	%
Age at surgery (years)	Mean ± SD	77.0 ± 10.4	
	Range	51–97	
Gender	Male/Female	30/25	54.5/45.5
Treated Eye	OD/OS	33/22	60.0/40
Lens Status	Phakic/Pseudophakic	1/54	1.8/98.2
Angle Characteristics	Open	55	100.0
Diagnosis	Pigment Dispersion Syndrome	4	7.3
	Pseudoexfoliation	2	3.6
BCVA 20/20 or better		14	25.5
BCVA 20/40 or better		42	76.4

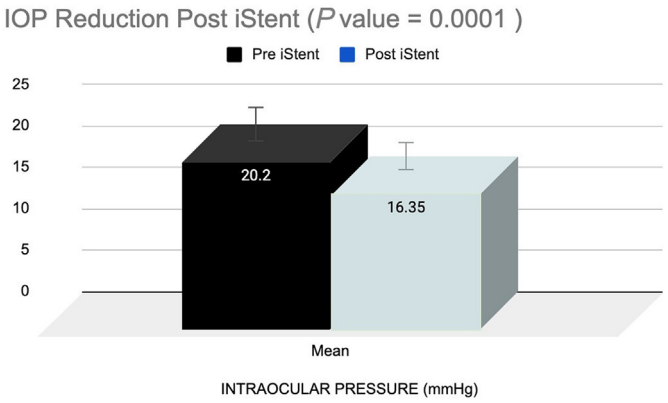

Fig. 1. The mean intraocular pressure reduced from 20.2 mmHg preoperatively to 16.35 mmHg post operatively.

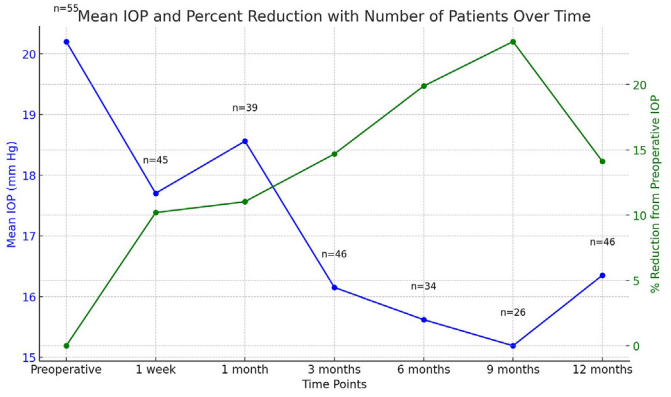

Fig. 2. Mean intraocular pressure at different time points post iStent inject (blue) and percentage reduction from preoperative intraocular pressure highlighted as green.

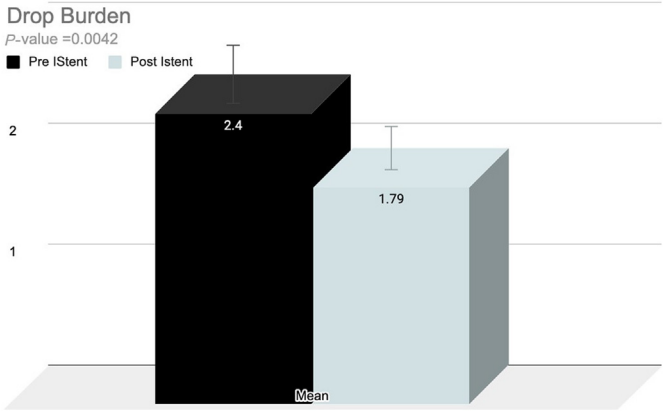

Fig. 3. The average number of eyedrops reduced to 1.79 post operatively.

Over the 12-month period, there was no significant difference observed ($P = 0.033$) between preoperative (0.29 ± 0.35 Log MAR) and postoperative (0.26 ± 0.55 Log MAR) best-corrected visual acuity (BCVA). The vision did not deteriorate in 72.3% (n = 34) of eyes at the 12-month follow-up. Table 3 outlines the progression of visual acuity from 1 month to 12 months after the surgery.

4. Discussion

The current literature on iStent Inject is primarily based on studies

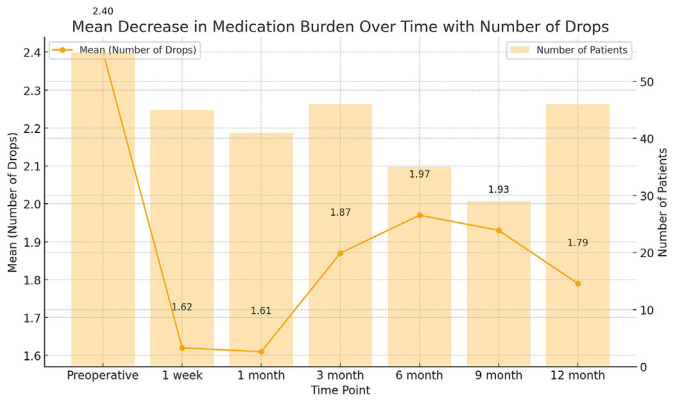

Fig. 4. The mean number of eyedrops preoperatively were 2.4 which reduced postoperatively, as depicted in the figure.

Table 2
Intraoperative and Postoperative surgical complications.

Event	Incidence (n = 22)	% of Sample (n = 55)
Stent malpositioned	3	5.5
Stent over implanted	5	9.1
Steroid responder	9	16.4
Postop CRVO	2	3.6
Iris prolapse	1	1.8
Corneal folds	1	1.8
Posterior capsular opacification	1	1.8

with stringent patient selection criteria, typically focusing on individuals with mild to moderate primary open-angle glaucoma (POAG) and ocular hypertension.[11,12] This study aimed to investigate the real-world application of iStent inject in a broader glaucoma patient population with open angles, aiming to achieve target IOP and reduce medication usage. By assessing the effectiveness and safety outcomes of iStent inject implantation in patients with a significant preoperative medication burden and surgical history in a real-world ophthalmology setting, this study provides valuable insights for general and specialized clinicians seeking treatment options for their glaucoma patients.

The use of minimally invasive devices like iStent inject offers advantages over traditional medication therapy and conventional surgical interventions in managing IOP in glaucomatous eyes. Challenges such as poor drop compliance impacting IOP control and the associated risk of disease progression highlight the importance of effective treatment strategies.[13] Even in patients with good drop compliance, IOP fluctuations associated with normal diurnal variations increases the risk of optic nerve damage in patients with glaucomatous disc changes.[14] Also, Muniesa et al. found significantly fewer IOP fluctuations in patients treated surgically compared with topical drop treatment for glaucoma, suggesting that surgical treatments have less IOP variability.[15] Minimally invasive devices have been shown to offer more stable IOP control compared to topical drops, potentially reducing IOP fluctuations and improving ocular surface health.[16]

The results of this study demonstrate that iStent Inject, when combined with cataract surgery, effectively reduces both IOP and medication burden. The reduction in mean IOP postoperatively at 6 and 12 months, along with the decrease in medication usage, underscores the efficacy of this approach. The study's findings align with similar research on second-generation iStent Inject trabecular bypass stents combined with cataract surgery for open-angle glaucoma.

While this retrospective study lacks a control group and specific postoperative medication guidelines, it provides valuable real-world data on the outcomes of iStent inject procedures. Despite its limitations, such studies offer practical insights for clinicians managing diverse glaucoma patient populations. Future research, including multicenter randomized controlled trials, can further enhance our understanding of the efficacy and safety of iStent inject in different clinical settings.

In this single centre, single surgeon (IM) study, reduction in IOP and medication burden are in line with the outcomes of similar studies done for evaluation of second-generation iStent Inject trabecular bypass stents combined with cataract surgery for open-angle glaucoma.[17–19] Mean IOP was lowered by 4.58 mm Hg (19.88%) and 3.85 mm Hg (14.6%) postoperatively at 6 and 12 months, respectively, which is a significant IOP reduction in the background of mean preoperative IOP of 20.2 ± 6.4 mm Hg. The overall reduction of intraocular postoperatively is depicted in Fig. 5. Although it is comparable to most existing studies of trabecular bypass stents, the cohort's low mean preoperative IOP makes it more difficult to achieve large postoperative IOP reductions. We must take into consideration that progressive vision loss can be noted in many patients despite the patients having IOP in a normal range and target IOP needs to be individualized based on serial visual fields, retinal nerve fibre layer analysis and disc changes for every patient being followed up for glaucoma.[20,21]

Concerning medication use, the mean drop medication burden was 2.4 ± 0.91 preoperatively which reduced significantly to 1.79 ± 1.18 medications at 12 months in iStent inject eyes (25.0% reduction, $P < 0.0042$). Twenty-three eyes (47%) of eyes at 12 months were noted to have a reduction in the number of medications compared to preoperative medications used and 41.6% (n = 20) eyes had no change in medication postoperatively at 12 months. Eight eyes (14.5%) did not require any form of medication to achieve the target IOP at 12 months. Prior studies have demonstrated that more than one topical drug is

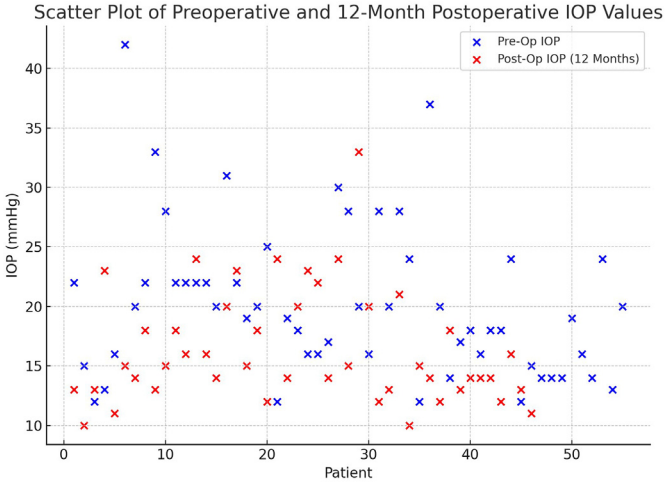

Fig. 5. Scatter plot showing preoperative intraocular pressures and post operative intraocular pressures at 12 months.

Table 3
Best corrected visual acuity (Log MAR) at each follow-up visit.

	Preoperative	1 week	1 month	3 month	6 month	9 month	12 month
n	55	46	40	46	34	27	47
Range (LogMAR)	−0.1 to 1.8	−0.1 to 2.3	−0.1 to 1.778	−0.2 to 1.5	−0.1 to 2.3	−0.075 to 0.2	−0.08 to 2.8
Mean BCVA (LogMAR)	0.291	0.30	0.219	0.15	0.26	0.36	0.26
SD	0.3585	0.48	0.37	0.34	0.52	0.69	0.55

associated with worse patient adherence and in this study, the percentage of patients on two medications decreased from 78.1% (n = 45) preoperatively to 56.2% (n = 29) at 1 year.[22] Also, the use of multiple topical medications is associated with greater ocular surface toxicity, reduced quality of life and also poorer outcomes in trabeculectomy procedures if required in advanced glaucoma.[23]

Visual acuity outcomes in this study are comparable to other similar published studies with patients showing no significant deterioration of visual acuity at 1 year follow up. (Preoperative 0.29 ± 0.35 Log MAR and postoperative 0.26 ± 0.55 Log MAR BCVA).[18,19]

There was no statistically significant mean visual gain recorded post operatively, due to presence of preexisting advanced glaucomatous optic neuropathy. Three patients were noted to have advanced glaucoma, two had undergone trabeculectomy prior to iStent inject procedure. Additionally, three patients required trabeculectomy after iStent placement to achieve target intraocular pressure due to worsening glaucomatous optic disc changes. Furthermore, two patients developed retinal vein occlusion with associated macular edema post-iStent surgery, and one patient experienced posterior capsular opacification. These factors likely contributed to the limited visual improvement observed in this cohort.

The safety profile in this study was comparable and in line with prior studies evaluating the first and second-generation devices (iStent and iStent inject, respectively).[24,25] There were no cases of postoperative hypotony. Postoperatively 16.4% of cases were noted to be steroid responders which eventually improved on stopping steroids. However, it should be noted that patients were continued on their preoperative glaucoma medications until 1 week, which may have mitigated any post-operative IOP spikes in the first week postoperatively. In addition, none of the eyes underwent an additional glaucoma procedure through 1 year follow up period.

This was a single surgeon (IM) study with extensive experience in implanting first-generation iStent devices, which has likely lessened any early learning difficulties with the second-generation device iStent inject implants. The overall IOP lowering effect in this study is better than single iStent implant as reported in the literature at six months in which a mean reduction of 3.7 mmHg at 6 months postoperative was reported, compared to the 4.58 mmHg reduction noted in this study.[25] While both technologies demonstrated favorable IOP-lowering results, early data favor the results of the present study evaluating the iStent inject.

This study is a retrospective study and with no control group to compare is a major limitation of the study. Hence, this could be categorized as Category four evidence.[26] Also, no specific guidance was adopted on the decision to add or remove topical medication in the postoperative period. Additionally, retrospective analysis prevents uniform follow up of the study population and this contributes to missing data points. However, evidence generated from a real-world scenario in a retrospective study can give important insight into the outcomes of patients undergoing procedures like iStent inject.

Another limitation to this study is the selection bias because the treatment can be individualized and based on target IOP, an individual requiring single-digit IOP might be offered a filtering procedure like trabeculectomy as a first option. A multicenter randomized controlled trial can generate better evidence but are restricted by the strict inclusion and exclusion criteria, restricted population and need of long term follow up of patients. The evidence generated in such retrospective studies would be expected to be more generalizable to current practicing ophthalmologists with diverse patient populations due to the heterogeneous group of glaucoma patients.

5. Conclusions

In conclusion, this study demonstrated significant and sustained reductions in both IOP and medication burden through 12 months postoperatively after implantation of 2 s-generation trabecular micro-bypass stents with cataract surgery, along with a very favorable safety profile. Also importantly, the study highlights these results in patients in a real-world clinical setting and with a clinically variable patient cohort, who were under a considerable preoperative drop load and in some cases prevalence of prior glaucoma surgery. With the influx of more MIGS devices as surgical options, ongoing and future clinical studies relating to iStent inject will be very relevant for defining the safety and efficacy of this device in long term and help comparison other MIGS devices that target the same anatomical space. Additional data collection and studies will ultimately be important for validating these early findings, but the results thus far are promising. This diversity in the study population in our study and real-world setting could make the data more representative of real-life clinical populations than many product registration trials. Thus, the study provides a useful reference for both clinicians and patients who are evaluating their glaucoma treatment options.

Study approval

The authors confirm that any aspect of the work covered in this manuscript that involved human patients or animals was conducted with the ethical approval of all relevant bodies and the study was performed in accordance with the Declaration of Helsinki.

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Declaration of competing interest

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.

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Abbreviations

POAG	Primary open angle glaucoma
IOP	Intraocular Pressure
OHT	Ocular hypertension
PXG	Pseudoexfoliation Glaucoma
PD	Pigment dispersion
NTG	Normal tension glaucoma
CCT	Central corneal thickness
PACG	Primary angle closure glaucoma
BCVA	Best corrected visual acuity
MIGS	Micro Invasive Glaucoma Surgery

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