

Two-Year Comparative Outcomes of First- and Second-Generation Trabecular Micro-Bypass Stents with Cataract Surgery

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Introduction: This retrospective comparative study assessed real-world effectiveness and safety of first-generation (iStent®) and second-generation (iStent inject®) trabecular micro-bypass stents with cataract surgery in patients with open-angle glaucoma (OAG).

Material and Methods: Through a 24-month postoperative follow-up, the effectiveness was quantified by intraocular pressure (IOP) reduction; mean glaucoma medication reduction; proportional analysis of eyes meeting IOP cutoffs (<18, <15, <12 mmHg) either with or without medications; and proportional analysis of medication burden. Safety measures included visual acuity, adverse events, and secondary surgery.

Results: A total of 82 consecutive eyes (39 iStent, 43 iStent inject) with a 24-month follow-up were analyzed. Most eyes (74.4%) had primary open-angle glaucoma, with the remainder having pseudoexfoliative or pigmentary glaucoma; all eyes had mild-to-moderate disease. At 24 months postoperative, the mean IOP was lower, and the percent reduction from baseline was greater, in iStent inject eyes (26.0% reduction, 17.7mmHg to 13.1mmHg) than in iStent eyes (9.8% reduction, 16.4mmHg to 14.8mmHg) (between-groups comparison, $p=0.019$). Within each group, the postoperative IOP reduction was greater in eyes with higher baseline IOP ($p<0.001$). Medication burden decreased significantly in both groups, from 1.74 to 0.51 mean medications for iStent (70.7% reduction, $p<0.0001$), and 2.19 to 0.65 for iStent inject (70.3% reduction, $p<0.0001$). Both groups exhibited excellent safety.

Conclusion: iStent or iStent inject with phacoemulsification produced significant IOP and medication reductions, with effects enduring for two years. IOP reductions were greater for iStent inject than for iStent. Within each group, higher preoperative IOP was associated with greater postoperative IOP reduction.

Keywords: iStent, iStent inject, trabecular micro-bypass, micro-invasive, MIGS

Introduction

Over the past decade, there has been a considerable expansion in the number of medical and surgical modalities available to treat glaucoma, the top cause of irreversible blindness around the world.¹ Treatments can range from topical medications (conservative) to filtration surgeries such as trabeculectomy and tube-shunt implantation (more invasive). As an intermediate intervention along this treatment continuum, an increasingly utilized option is micro-invasive glaucoma surgery (MIGS). Although MIGS procedures typically do not achieve the same dramatic intraocular pressure (IOP) reduction as traditional filtration surgeries, they do not carry the same risk of sight-threatening complications (eg, endophthalmitis,

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hypotony, choroidal detachment or effusion, bleb-related infections, etc.).^{2–4} In the large segment of patients whose disease does not yet warrant the risk of filtration surgery, MIGS procedures can offer a lower-risk, adequately efficacious treatment option.

The first United States Food and Drug Administration (FDA)-approved MIGS device, the iStent, as well as the second-generation iStent inject, both act upon the natural physiologic trabecular outflow pathway in patients with open-angle glaucoma (OAG). By creating a patent conduit between the anterior chamber and Schlemm's canal (and thereby to the episcleral venous plexus), the stents are designed to bypass the diseased trabecular meshwork into which they are placed. The iStent and iStent inject stents are composed of the same biocompatible, implant-grade titanium, and share the same mechanism of action; however, a number of key attributes distinguish the two devices. The most salient differences include the presence of two (iStent inject) versus one (iStent) stent, to enable access to more collector channels; four outlet lumens (iStent inject) versus one (iStent), for multidirectional aqueous outflow; and a straightforward (iStent inject) versus angled (iStent) surgical approach, for easier implantation. A substantial body of evidence exists for both devices, including studies in patients with various glaucoma subtypes, severities, and ethnicities; in stand-alone usage or combined with phacoemulsification; in real-world and FDA-trial settings; and in ancillary areas of research such as cost-effectiveness, ocular surface disease, refractive neutrality, and patient quality of life.^{5–40}

Three prior publications, including two from the authors^{38,39} and one by Manning in Australia,⁴⁰ compared outcomes of either device with cataract surgery in their respective patient populations. Results across the studies showed favourable safety and efficacy of both devices, while consistently demonstrating greater benefits for iStent inject over iStent in terms of mean IOP reduction, attainment of prespecified IOP endpoints, mean medication burden, medication reduction from baseline, and percent of patients becoming medication-free. The studies also showed highly favourable safety outcomes which have come to characterize both devices.

The purpose of the present study is to evaluate the safety and effectiveness of iStent and iStent inject in a larger and longer-term (two-year) cohort of OAG patients within the author's real-world patient population. This report constitutes the first two-year comparative analysis of the two devices to-date, providing information

with direct clinical relevance to practicing surgeons and their patients.

Materials and Methods

Study Design and Patient Population

In this longitudinal retrospective study, we evaluated all consecutive eyes that underwent implantation of either iStent or iStent inject combined with cataract surgery. All surgeries were performed in a single centre by one surgeon (R.G.). Choice between implants was largely based on the availability of the different implants on the Brazilian market. From June 2017 to November 2017, only first-generation trabecular micro-bypass was available for use. After the second-generation implant was approved for use (November 2017), the majority of cases migrated to it. In infrequent cases, patients' ability to pay for either device influenced implant selection. No clinical variable, such as level of IOP or glaucoma stage, drove the indications for either implant.

All patient charts were assessed for potential inclusion in the cohort using the following inclusion criteria: iStent or iStent inject surgery with phacoemulsification cataract surgery; age >18 years old; mild to moderate OAG [mean deviation (MD) no worse than -12 dB in Humphrey Visual Field Test]; current treatment with 0 to 4 glaucoma medications; surgery from June 2017 to June 2018 (ie, having at least 24 months of follow-up); and no significant ocular comorbidities that would confound glaucoma parameters. Exclusion criteria included follow-up less than 24 months; chronic or acute intraocular inflammation; angle closure; and the surgeon's first 10 iStent cases and first 5 iStent inject cases (to minimize any potential learning-curve bias). The study was performed in accordance with the ethical standards of the Declaration of Helsinki (as revised in Brazil 2013), including informed consent of patients; it was approved by the Ethics Committee of the Santa Casa de Misericórdia de Juiz de Fora.

Outcome Measures and Statistical Analysis

In addition to the demographic data of patients (age, sex, race, type of glaucoma, glaucoma stage), we evaluated the change in IOP, number of glaucoma medications, and visual acuity from the preoperative period to the end of the follow-up. Effectiveness outcomes included mean IOP reduction (%); reduction in mean number of medications (%); rates of "qualified success" (with adjunctive glaucoma medications as needed) at different IOP levels (IOP < 18 mmHg, <15

mmHg, <12 mmHg); rates of “unqualified success” (with no adjunctive glaucoma medications) at different IOP levels (IOP < 18 mmHg, <15 mmHg, <12 mmHg); and survival analysis of the probability of qualified and unqualified success at IOP < 18 mmHg through 2 years postoperative. Safety outcomes included visual acuity; intra- and post-operative adverse events; and secondary glaucoma interventions.

All numerical variables were tested for normality. For variables with normal distribution, a Student's *t*-test was used for comparisons. For non-normal distribution, a non-parametric test was used (Kruskal–Wallis or Mann–Whitney test). Chi-square testing was used for the analysis of categorical variables. A *p*-value of <0.05 was considered statistically significant. All statistical analyses were performed using IBM SPSS Statistics 25 (IBM Corp., Armonk, NY, USA).

Device Description and Implantation Technique

Figure 1 depicts the iStent (containing 1 stent) and iStent inject (containing 2 stents) trabecular micro-bypass systems with their respective dimensions. When implanted through the trabecular meshwork into Schlemm's canal,

the stents are designed to increase outflow of aqueous humour from the anterior chamber and thereby decrease IOP. The implantation procedure for each device has been detailed previously.^{5,19} In brief, the surgeon first places the injector through the existing phacoemulsification incision (or makes a new smaller peripheral clear corneal incision if stent implantation is completed as a standalone procedure). Next, the injector is advanced across the anterior chamber to the nasal angle, where the stent is placed into the trabecular meshwork (using a slightly angled approach for iStent or a flush straightforward approach for iStent inject). Then, in the case of an iStent inject implantation, the injector is repositioned within the anterior chamber (without exiting the eye) and a second stent is implanted approximately two clock hours from the first. At the close of either procedure, the stent position and stability are confirmed via intraoperative gonioscopy, the viscoelastic is removed, and the wound patency is ensured. Following surgery, patients were prescribed a topical antibiotic (Moxifloxacin, 4 times per day for one week) and a topical anti-inflammatory (Dexamethasone, 4 times per day and tapering over four weeks).

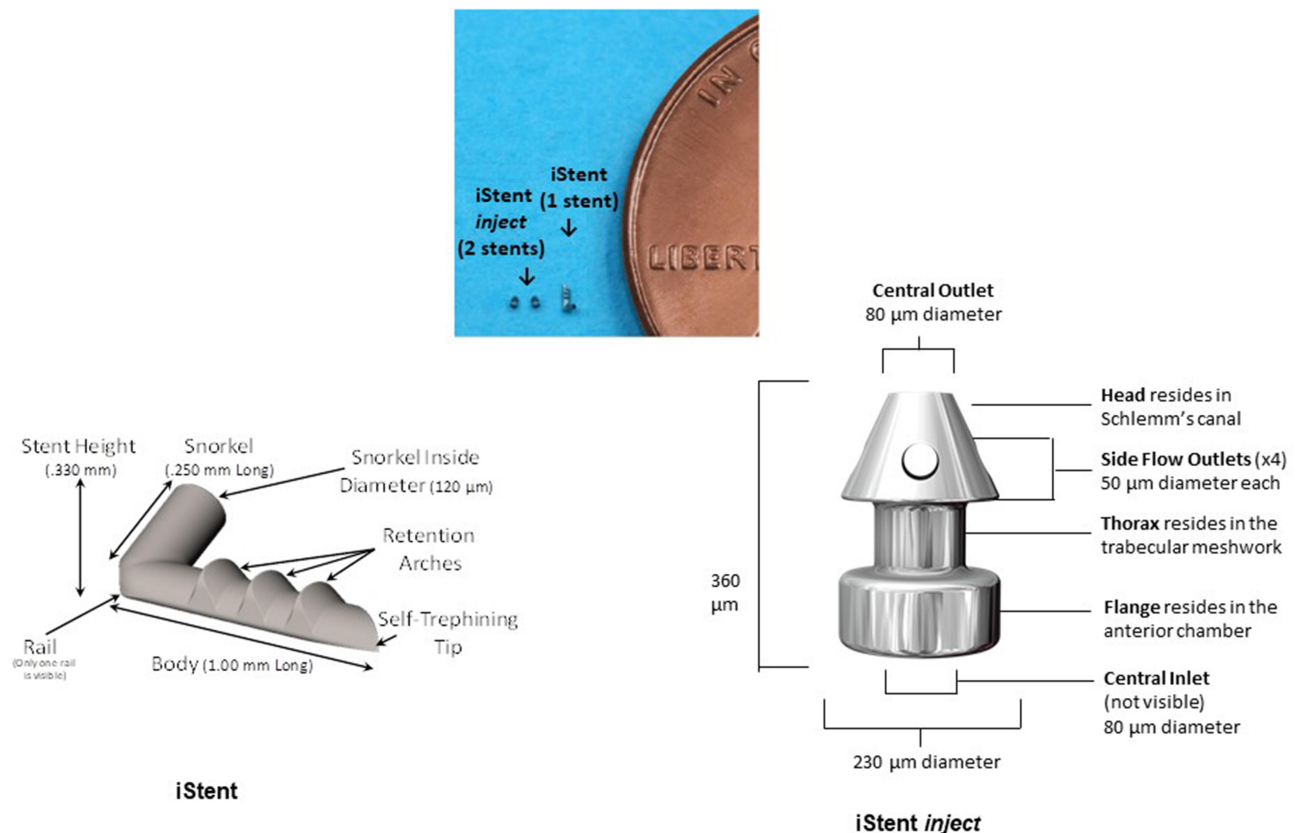


Figure 1 iStent® (left) and iStent inject® (right) trabecular micro-bypass stent systems. Image courtesy of Glaukos Corporation (229 Avenida Fabricante, San Clemente, CA 92672; copyright permission March 1, 2021).

Results

A total of 82 eyes from 82 patients satisfied the inclusion and exclusion criteria and were included in this analysis. Of note, although the present study and the prior two reports^{38,39} were drawn from the same patient base, each manuscript has analyzed a consistent set of patients reaching 6, 12, or 24 months of follow-up by the time of manuscript drafting, respectively, and thus their baseline demographics and post-operative outcomes are not identical.

In the present 24-month consistent cohort, baseline mean \pm standard deviation (SD) age was 70.1 ± 9.5 years (range 42–87), with the majority of patients being female (70.27%) and Caucasian (82.9%). Glaucoma severity was mild in 79.3% and moderate in 20.7% of eyes, according to the Hodapp-Parrish-Anderson visual field criteria (mild, MD no worse than -6 dB; moderate, MD worse than -6 dB but no worse than -12 dB; severe, MD worse than -12 dB).⁴¹ Approximately three-fourths (74.4%) of eyes had a diagnosis of primary open-angle glaucoma (POAG), with the remainder consisting of pseudoexfoliation glaucoma (PXG) and pigmentary glaucoma (PG).

Out of the study population, the iStent group comprised 39 eyes (47.6%) and the iStent inject group

comprised 43 eyes (52.4%). Table 1 presents the comparison between groups. The groups were well-balanced according to baseline IOP, race, laterality (right or left eye), type of glaucoma, glaucoma stage, and baseline visual acuity. The groups were statistically different according to mean age (the iStent inject group was an average of 9 years older; not independently clinically significant); gender (the iStent group had a higher proportion of female patients; not independently clinically significant); and baseline number of medications (2.2 mean medications in iStent inject eyes and 1.7 medications in iStent eyes).

IOP Results

Prior to surgery, the mean IOP was higher (although not significantly) in iStent inject eyes than in iStent eyes (17.7 mmHg vs 16.4 mmHg, respectively; $p=0.147$). However, by 12 months postoperative, the mean IOP was lower, and the percent reduction was greater, in iStent inject eyes (26.0% reduction, from 17.7 mmHg to 13.1 mmHg) than in iStent eyes (11.0% reduction, from 16.4 mmHg to 14.8 mmHg) (between-groups comparison of percent reduction, $p=0.002$). This between-group difference persisted through

Table 1 Baseline Characteristics for Each Group

Characteristics		iStent + Cataract Surgery n=39	iStent Inject + Cataract Surgery n=43	p-value
Age (mean \pm SD), years		65.7 \pm 9.3	74.1 \pm 7.8	<0.001 ^a
Baseline IOP, mmHg		16.4 \pm 3.8	17.7 \pm 4.0	0.147 ^a
Baseline number of medications		1.7 \pm 0.8	2.2 \pm 1.0	0.035 ^a
Race	Caucasian	74.4%	90.7%	0.058 ^b
	African descent or mixed descent	25.6%	9.3%	
Sex	Male	17.9%	39.5%	0.032 ^b
	Female	82.1%	60.5%	
Glaucoma Stage	Early	84.6%	74.4%	0.255 ^b
	Moderate	15.4%	25.6%	
Laterality	OD	51.3%	51.2%	0.991 ^b
	OS	48.7%	48.8%	
Type of Glaucoma	POAG	64.1%	83.7%	0.057 ^b
	Other OAG	35.9%	16.3%	
Baseline visual acuity	20/30 or better	53.8%	62.8%	0.673 ^b
	20/40 to 20/100	38.5%	32.6%	
	20/200 or worse	7.7%	4.7%	

Notes: ^aStudent *T* test; ^bChi-square test.

Abbreviations: SD, standard deviation; IOP, intraocular pressure; OD, right eye; OS, left eye; POAG, primary open-angle glaucoma; OAG, open-angle glaucoma.

24 months postoperative, when iStent inject eyes continued to display a 26.0% IOP reduction (from 17.7 mmHg to 13.1 mmHg) versus a 9.8% reduction in iStent eyes (16.4 mmHg to 14.8 mmHg) (between-groups comparison of percent reduction, $p=0.019$). Figure 2 depicts mean IOP throughout the 24-month follow-up period for each study group. Table 2 provides the complete listing of mean IOP values for each time point, including statistical comparisons between and within groups. Reduction in IOP values from baseline achieved statistical significance at all time points (from Day 1 to Month 24) for both groups, with the exception of Day 15 in the iStent group. Figure 3 specifically highlights analyses at the 12-month and 24-month time points versus baseline.

Additional analyses were completed with stratification by baseline IOP: 40 eyes with baseline IOP ≤ 16 mmHg (23 iStent, 17 iStent inject); 17 eyes with baseline IOP 17–18 mmHg (6 iStent, 11 iStent inject); and 25 eyes with baseline IOP ≥ 19 mmHg (10 iStent, 15 iStent inject) (Chi-Square: $p=0.204$). Within both the iStent and iStent inject groups, postoperative IOP reduction was significantly greater in eyes with higher baseline IOP ($p<0.001$ in each group) [Figure 3].

Table 3 shows the rates of achieving different levels of target postoperative IOP for each group, either by allowing

for medication usage (“qualified success”) or with no medications (“unqualified success”). At 24 months after surgery, both groups had higher proportions of eyes achieving the success criteria compared to baseline; the increases reached statistical significance for most cutoffs in iStent eyes, and for all cutoffs in iStent inject eyes.

A survival analysis also was conducted using Kaplan-Meier survival curves (Figure 4A and B). Mean survival time for an IOP < 18 mmHg with or without medications was 25.4 months (95% CI: 20.6–30.2) for the iStent group and 25.3 months (95% CI: 22.4–28.3) for the iStent inject group. Mean survival time for an IOP < 18 mmHg with no medications was 21.9 months (95% CI: 16.8–27.0) for the iStent group and 21.4 months (95% CI: 17.7–25.2) for the iStent inject group.

Probability of success for an IOP < 18 mmHg with or without medications was 66.7% and 81.4% ($p=0.126$, Log Rank, Mantel-Cox) for the iStent and iStent inject groups, respectively. Probability of success for an IOP < 18 mmHg with no medications was 56.4% and 67.4% ($p=0.305$, Log Rank, Mantel-Cox) for the iStent and iStent inject groups, respectively.

Although sample size was limited, an exploratory subgroup analysis was conducted of eyes with secondary

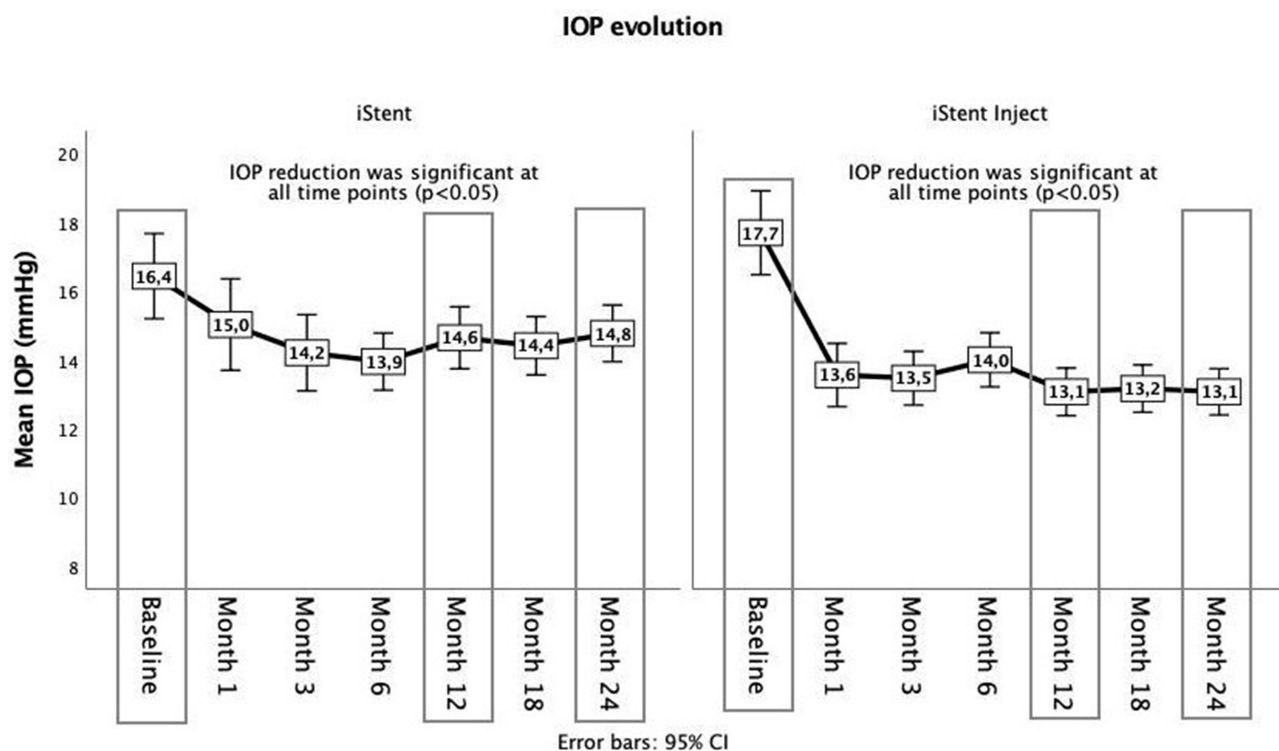


Figure 2 Mean IOP from baseline through 24 months in each study group.

Table 2 Mean Intraocular Pressure Through 24 Months, with Comparisons Between and Within Study Groups

Time Point	iStent + Cataract Surgery n=39	iStent Inject + Cataract Surgery n=43	Comparisons Between Groups ^b
Baseline IOP	16.4 mmHg	17.7 mmHg	0.147
Day 1	14.2 mmHg	12.7 mmHg	0.107
Comparison vs Baseline ^a	0.001	<0.001	
Day 15	15.5 mmHg	14.7 mmHg	0.370
Comparison vs Baseline ^a	0.211	<0.001	
Month 1	15.0 mmHg	13.6 mmHg	0.066
Comparison vs Baseline ^a	0.040	<0.001	
Month 3	14.2 mmHg	13.5 mmHg	0.266
Comparison vs Baseline ^a	0.002	<0.001	
Month 6	13.9 mmHg	14.0 mmHg	0.928
Comparison vs Baseline ^a	0.001	<0.001	
Month 9	14.6 mmHg	13.6 mmHg	0.204
Comparison vs Baseline ^a	0.033	<0.001	
Month 12	14.6 mmHg	13.1 mmHg	0.006
Comparison vs Baseline^a	0.003	<0.001	
Month 18	14.4 mmHg	13.2 mmHg	0.023
Comparison vs Baseline ^a	0.004	<0.001	
Month 24	14.8 mmHg	13.1 mmHg	0.002
Comparison vs Baseline^a	0.015	<0.001	

Notes: Bold text indicates key data points (Baseline, Month 12, and Month 24); ^aStudent paired t-test; ^bStudent two-sample t-test.

Abbreviation: IOP, intraocular pressure.

glaucoma (PXG or PG, n=21) that underwent implantation of either stent model. At 24 months following surgery, mean IOP in this subgroup reduced by 22.8% versus baseline, from 18.4 mmHg to 14.2 mmHg ($p=0.001$). This was generally consistent with the outcomes seen in the POAG subgroup (n=61), which experienced an 18.1% IOP reduction versus baseline, from 16.6 mmHg to 13.6 mmHg ($p<0.001$).

Reduction in Medications

The reduction in mean number of medications versus baseline achieved statistical significance at all time points ($p<0.001$) during 24-month follow-up for both groups (Figure 5 and Table 4). At both Month 12 and Month 24, the groups achieved similarly significant reductions in mean number of medications versus baseline. The iStent group

experienced a 73.6% medication reduction at 12 months (from 1.74 to 0.46 mean medications, $p<0.001$), and a 70.7% reduction at 24 months (from 1.74 to 0.51 mean medications, $p<0.001$); the iStent inject group experienced a 70.3% medication reduction at 12 months (from 2.19 to 0.65 mean medications, $p<0.001$) as well as at 24 months. These reductions vs. baseline were statistically similar in the two groups at both time points ($p=0.841$ and $p=0.748$ for between-groups comparison of percent reduction at the 12- and 24-month time points, respectively).

Figure 6A–B shows the distribution of number of medications at baseline and at 24 months. Preoperatively, 59.0% of iStent eyes and 69.8% of iStent inject eyes were on 2 or more glaucoma medications; by 24 months, this had decreased to 17.9% of iStent eyes and 20.9% of iStent inject eyes. At 24 months, 71.8% of iStent eyes and 65.1% of iStent

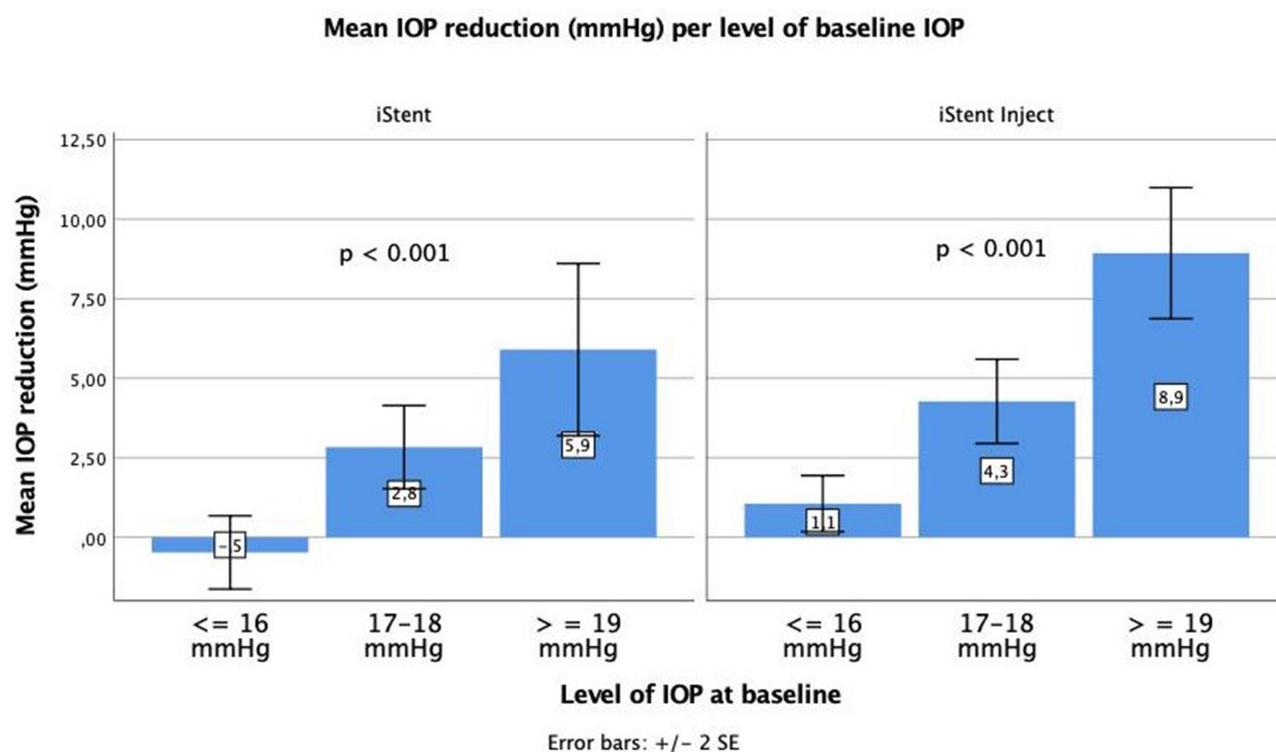


Figure 3 Mean IOP reduction (mmHg) according to different levels of baseline IOP.

inject eyes were medication-free ($p=0.832$ for between-groups comparison), versus 5.1% of iStent eyes and 2.3% of iStent inject eyes at baseline.

Within the subgroup analysis of secondary glaucoma cases (PXG and PG, $n=21$), mean number of medications at 24 months reduced by 51.3% versus baseline, from 1.95 to 0.95 mean medications ($p<0.001$). In the POAG subgroup ($n=61$), the mean number of medications reduced by 75.8%, from 1.98 to 0.48 ($p<0.001$).

Visual Acuity Results

There was a significant improvement in the visual acuity in both groups after phacoemulsification-stent surgery. While 53.8% of iStent eyes and 62.8% of iStent inject eyes (between-groups comparison $p=0.673$) had a visual acuity of 20/30 or better at baseline, 82.1% of iStent eyes and 93.0% of iStent inject eyes (between-groups comparison $p=0.119$) attained this visual acuity level at 24 months. Within-group comparisons of 24-month visual

Table 3 Qualified and Unqualified Success Rates for Different IOP Targets

Success Criteria		iStent + Cataract Surgery n=39			iStent Inject + Cataract Surgery n=43			Between-Group Comparison at M24
		Baseline	Month 24	Within-Group Comparison (Baseline vs M24)	Baseline	Month 24	Within-Group Comparison (Baseline vs M24)	
IOP <18 mmHg	Qualified	71.8%	89.7%	0.092	48.8%	97.7%	<0.001	0.151
	Unqualified	2.6%	66.7%	<0.001	0.0%	65.1%	<0.001	0.534
IOP <15 mmHg	Qualified	33.3%	82.1%	<0.001	20.9%	90.7%	<0.001	0.206
	Unqualified	2.6%	66.7%	<0.001	0.0%	60.5%	<0.001	0.363
IOP <12 mmHg	Qualified	7.7%	12.8%	0.727	2.3%	37.2%	<0.001	0.011
	Unqualified	2.6%	2.6%	1.000	0.0%	14.0%	<0.001	0.071

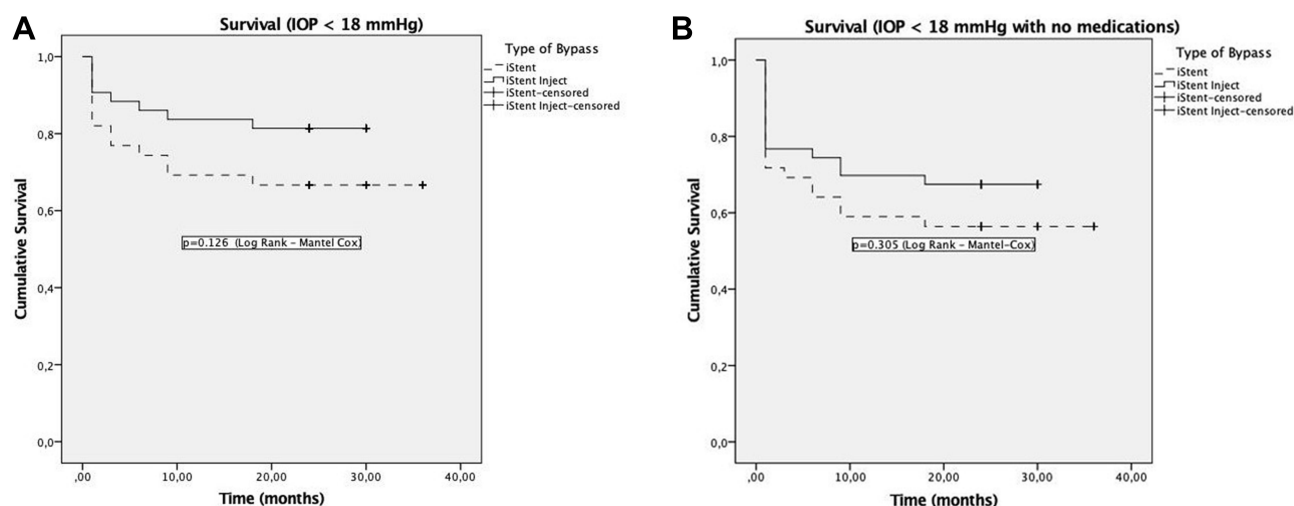


Figure 4 (A) Kaplan-Meier survival analysis for both groups for an IOP < 18 mmHg with or without medications. **(B)** Kaplan-Meier survival analysis for both groups for an IOP < 18 mmHg with no medications.

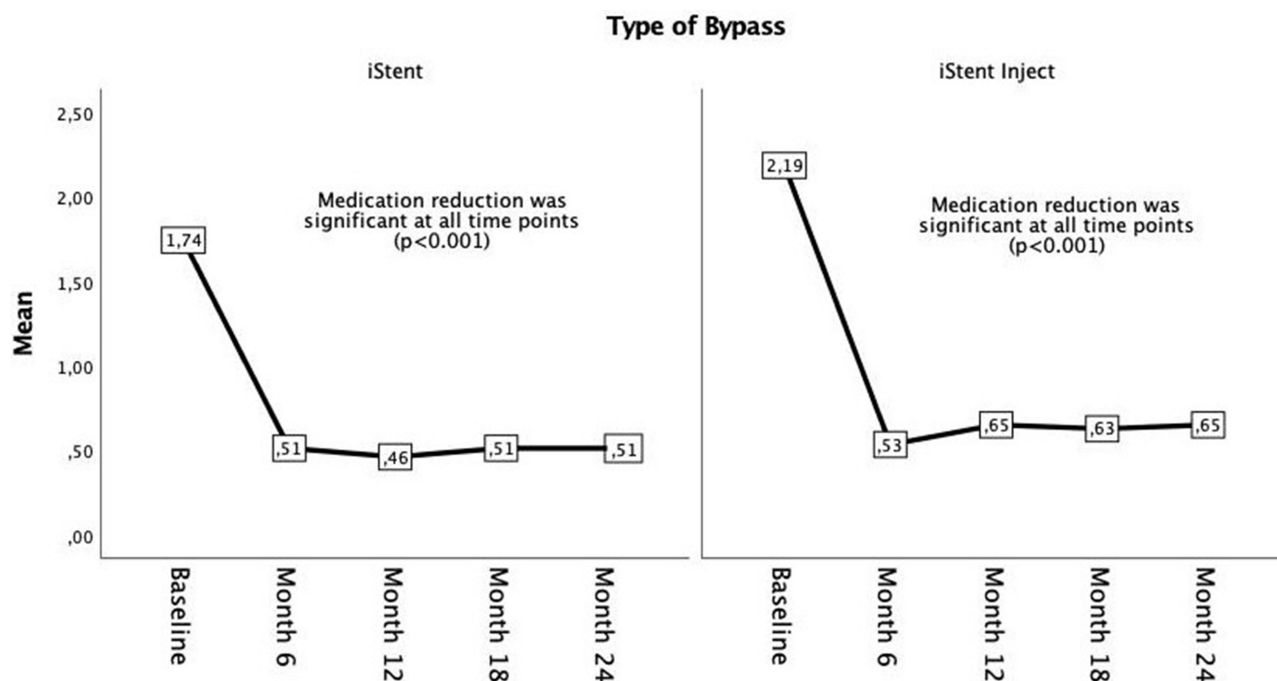


Figure 5 Mean number of medications from baseline to 24 months in each group.

acuity proportions versus baseline were significant for both groups ($p=0.018$ for iStent and $p=0.012$ for iStent inject).

Safety Results

Both groups demonstrated a high safety profile. Intraoperative complications were rare, occurring in 4 eyes in the iStent group (10.3%) and no eyes in the

iStent inject group (between-groups comparison $p=0.098$). The 4 iStent complications included three cases of excessive blood reflux and one case of stent malpositioning (under- or over-implanted, as identified by gonioscopic examination).

Postoperative adverse events also were infrequent, occurring in 4 eyes (10.3%) in the iStent group and 1 eye (2.3%) in the iStent inject group. In the iStent group, one eye had focal

Table 4 Mean Number of Medications Through 24 Months, with Comparisons Between and Within Study Groups

Time Point	Number of Medications per Eye		Comparisons Between Groups ^b
	iStent + Cataract Surgery n=39	iStent Inject + Cataract Surgery n=43	
BASELINE	1.74	2.19	0.035
Day 1	0.10	0.14	0.731
Comparison vs Baseline ^a	<0.001	<0.001	
Day 15	0.26	0.33	0.670
Comparison vs Baseline ^a	<0.001	<0.001	
Month 1	0.44	0.40	0.817
Comparison vs Baseline ^a	<0.001	<0.001	
Month 3	0.46	0.51	0.804
Comparison vs Baseline ^a	<0.001	<0.001	
Month 6	0.51	0.53	0.913
Comparison vs Baseline ^a	<0.001	<0.001	
Month 9	0.51	0.63	0.599
Comparison vs Baseline ^a	<0.001	<0.001	
MONTH 12	0.46	0.65	0.398
Comparison vs Baseline ^a	<0.001	<0.001	
Month 18	0.51	0.63	0.594
Comparison vs Baseline ^a	<0.001	<0.001	
MONTH 24	0.51	0.65	0.521
Comparison vs Baseline ^a	<0.001	<0.001	

Notes: Bold text indicates key data points (Baseline, Month 12, and Month 24). ^a Student paired t-test, ^b Student two-sample t-test.

Abbreviation: IOP, intraocular pressure.

peripheral anterior synechia occluding the internal ostium of the iStent, which was corrected by Nd:YAG laser goniosynechialysis with no resultant sequelae. Three other iStent eyes had uncontrolled IOP during follow-up (all of them between 3 and 6 months postoperative) and underwent filtration surgery: in two eyes due to steroid-induced IOP spike from systemic steroid use, which the patients required for pulmonary and rheumatologic diseases; and in one eye due to allergies to all ocular hypotensive agents and the need for more IOP reduction than what was achieved by the stent. In the iStent inject group, one eye had insufficient IOP control and underwent a filtration surgery at 3 months. The IOP and medication values recorded after filtration surgery in these four eyes were excluded from subsequent efficacy and survival curve analyses.

Discussion

This paper constitutes some of the first comparative two-year data on the first- and second-generation trabecular micro-bypass stents, iStent and iStent inject. Significant reductions in IOP and medications were observed with either device, along with a favourable safety profile. As with the one-year data, the IOP and medication reductions from baseline were significant in both groups, with greater gains observed after iStent inject than iStent. The degree of postoperative IOP reduction also was greater in eyes with higher preoperative IOP, as has been shown previously.^{10,12–14,21} Importantly, the outcomes in both groups were achieved in consecutive (all-comer) patients in the context of the surgeon's clinical practice, with the patient population including different glaucoma subtypes

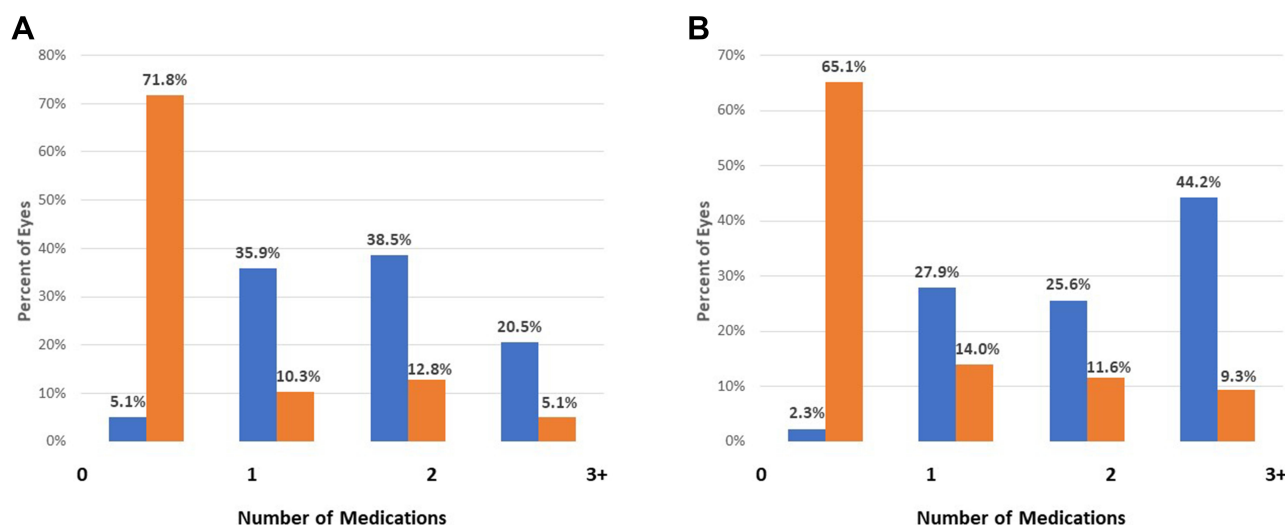


Figure 6 Distribution of number of medications at baseline and at 24 months, iStent group (A) and iStent inject group (B).

and severities. The subgroup analysis of secondary glaucoma cases (PXG and PG), although limited in size, revealed favourable IOP and medication reductions, consistent with previously published larger studies of the iStent specifically in these populations.^{12,13} Altogether, these study attributes reinforce the veracity and applicability of the data to the diverse real-world settings in which surgeons and patients make treatment decisions.

The IOP reduction following iStent inject was consistently greater than that of iStent. This between-group difference was apparent at 12 months and remained present to a similar or greater degree at 24 months. Higher proportions of iStent inject eyes than iStent eyes also met the prespecified effectiveness endpoints (IOP <18, 15, 12 mmHg) at 24 months. These between-group differences have meaningful consequences given that every 1 mmHg of IOP reduction has been shown to equate to a 10% lower risk of glaucoma development⁴² and a 10–19% lower risk of glaucoma progression.^{43,44} Alongside the reductions in IOP, both groups experienced significant reductions in medication burden from baseline. This was manifested not only in a decreased mean medication burden (from 1.74 to 0.51 medications in iStent eyes, and from 2.19 to 0.65 medications in iStent inject eyes), but also in a three-fold decrease in the proportion of eyes on ≥ 2 medications, and a 14- to 28-fold increase in the percentage of eyes becoming eyedrop-free versus baseline.

The benefits of medication reduction are widely varied and highly impactful. Topical medications are known to degrade the conjunctiva and increase the risk of future surgical failure.⁴⁵ Their effect is limited by relatively

high rates of eyedrop non-compliance, which increases the risk of visual loss and disease progression.⁴⁶ Even when perfect compliance is present, the diurnal IOP fluctuations of any non-surgical treatment may place patients at greater risk of disease progression.⁴⁷ Topical medications also are known to promote ocular surface disease (OSD) and dry eye,⁴⁸ and to diminish the quality of life (QoL).⁴⁹

Although the goal of medication reduction is important to all glaucoma patients, it is especially germane to patients undergoing MIGS procedures. MIGS patients typically have mild to moderate disease severity that does not necessitate the dramatic IOP reductions of traditional filtration surgeries, nor warrant the risks associated with such surgeries. In many of these patients, the primary goal of stent implantation may be medication reduction with its associated OSD and QoL benefits (provided that IOP stay at a similar or lower level than preoperative).

The impact of MIGS surgery on OSD and QoL is an increasingly important area of research. To date, one study has specifically examined the change in OSD,³¹ and one pivotal trial has analyzed the change in QoL,³⁷ following MIGS surgery and its attendant medication reductions; both studies were completed in eyes undergoing iStent or iStent inject implantation. The OSD analysis by Schweitzer et al showed significant improvements in objective examination findings and subjective symptom questionnaires following iStent or iStent inject implantation.³¹ The first QoL analysis within a MIGS pivotal trial, completed within the iStent inject trial, showed significantly higher rates of QoL and OSD

improvement in stent eyes than in control eyes.³⁷ In light of the findings of these two studies, the substantial medication reduction observed in the present study is particularly important and relevant.

There were certain limitations in the current 24-month analysis. The data were collected retrospectively and were drawn from a single surgeon and site. Preoperative mean IOP was slightly lower in the iStent group compared to the iStent inject group; although the difference was not statistically significant, it could have mildly influenced the percentage IOP reduction that could be reached postoperatively (given the previously discussed correlation between higher preoperative IOP and greater postoperative percentage reduction). Stent implantation was completed with concomitant cataract surgery, so the stent effect could not be isolated from the effect of cataract surgery. However, since each group would be affected by phacoemulsification equally, the between-group differences are still meaningful; and within each group, the preoperative measures of the patients could serve as their own control, so any preoperative-versus-postoperative comparisons remain relevant. Finally, the subgroup analysis of secondary glaucoma cases showed favourable preliminary trends, consistent with prior research,^{12,13} but further studies will be important to more fully assess stent performance in these subtypes.

Conclusions

In summary, this real-world retrospective analysis provides novel two-year information on the comparative safety and effectiveness of the first-generation iStent and second-generation iStent inject trabecular micro-bypass stents. Through 24 months postoperative, both devices produced sustained and significant reductions in IOP and medication burden, while maintaining favourable safety. Comparatively, the iStent inject group experienced consistently greater IOP reductions and higher proportions of eyes meeting the prespecified IOP endpoints than the iStent group. Within both groups, higher preoperative IOP was associated with greater postoperative IOP reductions. Mean medication reduction was similarly substantial in both groups (approximately 70% decrease from preoperative), with both groups also exhibiting a dramatic increase in the percent of eyes being medication-free.

Compliance with Ethics Guidelines

The study was performed in accordance with the ethical standards of the Declaration of Helsinki (as revised in

Brazil 2013), including informed consent of patients; it was approved by the Ethics Committee of the Santa Casa de Misericórdia de Juiz de Fora.

Authorship Verification

All authors contributed to data analysis, drafting or revising the article, have agreed on the journal to which the article will be submitted, gave final approval of the version to be published, and agree to be accountable for all aspects of the work.

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