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ORIGINAL RESEARCH

One-Year Comparative Evaluation of iStent or iStent *inject* Implantation Combined with Cataract Surgery in a Single Center

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ABSTRACT

Introduction: This retrospective consecutive case series assessed 12-month effectiveness and safety of iStent® or iStent *inject*® trabecular micro-bypass implants with cataract surgery in patients with open-angle glaucoma (OAG) in a real-world clinical setting.

Methods: Effectiveness outcomes consisted of intraocular pressure (IOP) reduction; glaucoma medication reduction; proportions of eyes achieving IOP < 18, < 15, or < 12 mmHg; and proportional analysis of medication usage. Safety outcomes included adverse events, secondary surgeries, and best-corrected visual acuity (BCVA).

Results: This evaluation included 58 eyes with OAG (35 iStent, 23 iStent *inject*), with 96.6% of eyes having mild or moderate glaucoma. Diagnoses included primary open-angle glaucoma (the majority; 72.4%), pseudoexfoliative glaucoma, and pigmentary glaucoma. Baseline mean IOP and medications were statistically comparable between groups: 16.1 ± 3.6 mmHg on a mean of 1.8 ± 0.8 medications in the iStent group, and 16.2 ± 3.1 mmHg on a mean of 1.7 ± 0.8 medications in the iStent *inject* group. Twelve months after stent-cataract surgery, mean IOP was significantly lower in the iStent *inject* group than in the iStent group (13.1 mmHg vs. 15.4 mmHg, respectively; $p < 0.001$), and the percent reduction in IOP from baseline was significantly greater in iStent *inject* eyes than in iStent eyes (19.1% vs. 4.3% reduction, respectively; $p < 0.001$). At 12 months postoperative, significantly greater proportions of iStent *inject* eyes than iStent eyes achieved IOP < 18 mmHg (100% vs. 80.0% of eyes, respectively; $p = 0.035$), IOP < 15 mmHg (73.9% vs. 34.3% of eyes, respectively; $p = 0.003$), and IOP < 12 mmHg (26.1% vs. 0% of eyes, respectively; $p = 0.002$). Meanwhile, both groups achieved significant medication reductions at 12 months vs. baseline (94.1% reduction in iStent *inject* eyes, $p < 0.0001$; and 72.2% reduction in iStent eyes, $p < 0.0001$), with the percent reduction being significantly greater in iStent *inject* eyes than in iStent eyes ($p = 0.023$). At 12 months, mean number of medications was significantly lower in iStent *inject* eyes than iStent eyes (0.1 vs. 0.5 medications, respectively; $p = 0.021$), and significantly

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more iStent *inject* eyes (95.7%) than iStent eyes (71.4%) were off medications entirely ($p = 0.021$). A similarly high safety profile was observed in both groups.

Conclusion: iStent or iStent *inject* implantation with cataract surgery resulted in substantial and safe reductions in IOP and medications through 12 months postoperative. Consistent with prior observations, greater efficacy was observed with iStent *inject* than with iStent.

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Keywords: Cataract; Glaucoma; Intraocular pressure; iStent; iStent *inject*; Medication; Microinvasive glaucoma surgery (MIGS); Safety; Second-generation; Trabecular micro-bypass

INTRODUCTION

Already the top cause of permanent blindness globally, glaucoma is expected to increase even further in prevalence in coming decades [1]. Currently, the central objective of all glaucoma treatments is to reduce intraocular pressure (IOP), which is the primary risk factor for the development and progression of glaucoma and visual field loss. Several foundational landmark studies soundly established the strong protective connection between lowering IOP and reducing glaucoma damage [2–5]. One of the studies, the Early Manifest Glaucoma Trial (EMGT), even assigned a numerical measure to this reduced risk: approximately 10% reduction in the risk of glaucoma progression for every 1 mmHg of IOP reduction [3].

A number of medical and surgical therapies are available to treat glaucoma, each of which has benefits and downsides. Conservative interventions typically include topical medications and/or laser trabeculoplasty procedures [6, 7]. Medications are reliably effective in reducing IOP and are usually the first-line intervention, but they are associated with side effects, ocular surface deterioration, costs, inconsistency with drop instillation, and regrettably low treatment adherence [8–12]. Laser procedures also are an effective early intervention, but their effects are known to decline over time, thereby posing a recurring challenge for patients with this lifelong disease [13]. Traditional incisional glaucoma surgeries such as trabeculectomy or tube implantation can produce dramatic IOP reduction, but they also carry a risk profile that includes sight-threatening complications such as hypotony maculopathy, choroidal detachment and effusion, endophthalmitis, anterior chamber collapse, and bleb-related infections or inflammation [14–16].

Micro-invasive glaucoma surgery (MIGS) has been developed and refined over the past decade to bridge the gap between medication and filtering surgeries [17]. The first Food and Drug Administration (FDA)-approved MIGS device, the iStent trabecular micro-bypass, as well as the more recently introduced iStent *inject* trabecular micro-bypass (Fig. 1), have been examined in a wide range of studies and clinical settings. The devices have been studied with and without cataract surgery, in various severities of glaucoma, in different types of glaucoma (e.g., primary open-angle glaucoma, POAG; pseudoexfoliative glaucoma, PXG; normal-tension glaucoma, NTG; combined-mechanism glaucoma, CMG) as well as in ocular hypertension [18–40]. The data have consistently shown favorable safety together with substantial and durable reductions in IOP and medications.

The present cohort includes consecutive cases of either the iStent (comprising one first-generation stent) or iStent *inject* (comprising two second-generation stents) trabecular micro-bypass implanted with concomitant cataract surgery. Both devices decrease IOP by creating a patent pathway (or pathways) through the trabecular meshwork into Schlemm's canal, thereby promoting egress of aqueous humor from the anterior chamber. The cohort's inclusion of both devices allows us to distinguish the effects of two stents versus one (iStent *inject* versus iStent, respectively), as well as to assess for any potential benefit of the design features of the newer iStent *inject* device. The current report draws data only from patients having 12 months of follow-up visits (consistent cohort, $n = 58$). A prior publication [40] showed outcomes for patients having 6 months of

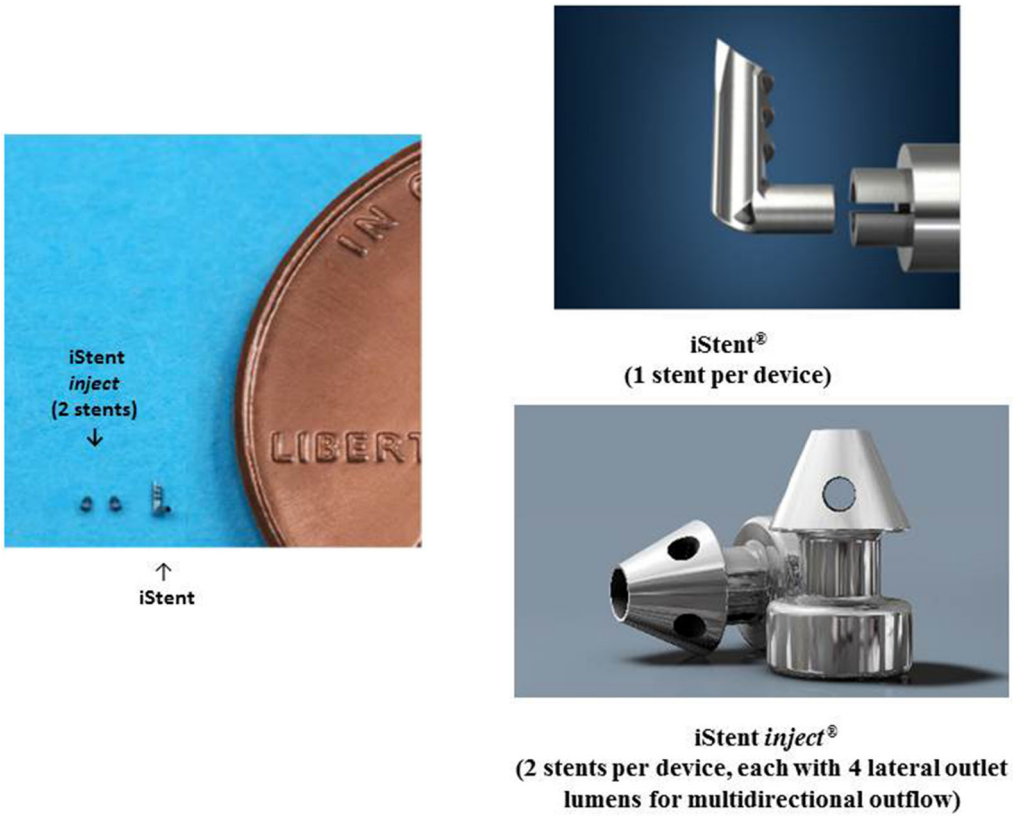

Fig. 1 iStent® and iStent *inject*® trabecular micro-bypass stents, with relative dimensions (image courtesy of Glaukos Corp., San Clemente, CA, USA)

follow-up visits (n = 73). Given that each report pertains to a consistent group of patients at a given point in time (6 months or 12 months), the 6- and 12-month analyses are not directly comparable.

The aim of the present study was to compare the 12-month performance and safety outcomes of iStent and iStent *inject* implantation in combination with cataract surgery in eyes with mild to moderate open-angle glaucoma. This report contributes one of the first datasets with side-by-side data on the two devices in a real-world clinical population.

METHODS

In this longitudinal retrospective study, we evaluated 12-month outcomes of consecutive eyes that underwent implantation of either iStent or iStent *inject* in combination with cataract surgery from June 2017 to June 2018. The choice between implants was based predominantly on the availability of the different implants on the Brazilian market. To eliminate any possible impact of a learning curve on outcomes, we excluded the first 10 iStent cases and the first 5 iStent *inject* cases from the cohort. All surgeries were performed in a single private practice ophthalmic surgery center by one surgeon (RG).

Inclusion criteria included age over 18 years, diagnosis of OAG, follow-up data through 12 months postoperative, cataract requiring surgery, and the need to reduce IOP or medications. Eyes were required to have anterior chamber angle grade of III or IV (per the modified Shaffer classification), where at least the scleral spur was visible under gonioscopic view. Preoperative glaucoma severity was classified using the Hodapp–Parrish–Anderson visual field criteria (mild, mean deviation (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]. We excluded eyes with shorter follow-up than 12 months.

Main outcome measures through 12 months included mean IOP and medications; percentage reduction in IOP and medications versus baseline; proportions of eyes with IOP < 18 mmHg, < 15 mmHg, or < 12 mmHg; and proportional analysis of medication usage. IOP was measured by Goldmann applanation. Safety assessments included intraoperative and postoperative adverse events, secondary surgeries, and best-corrected visual acuity (BCVA, Snellen). Gonioscopy was performed preoperatively and at every postoperative visit during follow-up in order to evaluate the angle and stent positioning.

We used the chi-square test and Student's *t* test, respectively, for the analysis of categorical and numerical variables. Statistical analysis was performed in SPSS. We considered a *p* value of 0.05 for statistical significance. All procedures were in accordance with the Institutional Review Board of the Paletta Guedes Eye Institute and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. Formal trial registration was not required for this retrospective analysis, given that it included only patients from the surgeon's real clinical practice who already received treatment.

RESULTS

All eyes underwent uncomplicated phacoemulsification cataract surgery, followed by implantation of either the iStent ($n = 35$) or the iStent *inject* ($n = 23$) trabecular micro-bypass. Preoperative demographics and ocular parameters are displayed in Table 1. Almost all eyes (96.6%) had mild or moderate glaucoma, and the predominant diagnosis was primary open-angle glaucoma (POAG, 72.4% of eyes), with the remaining eyes having pseudoexfoliative glaucoma (PXG) or pigmentary glaucoma (PG). At baseline, the groups were statistically comparable in nearly all parameters, including IOP, medications, and glaucoma stage. Baseline age was slightly higher in iStent *inject* eyes, and there were slightly more women in the iStent group.

Table 1 Baseline demographic and ocular characteristics

Characteristics	iStent + cataract surgery $n = 35$	iStent *inject* + cataract surgery $n = 23$	*p* value
Age (mean ± SD), years	67.8 ± 8.9	73.4 ± 7.4	0.013[a]
Baseline IOP, mmHg	16.1 ± 3.6	16.2 ± 3.1	0.882[a]
Baseline number of medications	1.8 ± 0.8	1.7 ± 0.8	0.565[a]
Race			
Caucasian	74.3%	91.3%	0.203[b]
African descent	25.7%	8.7%	
Gender			
Male	17.1%	43.5%	0.038[b]
Female	82.9%	56.5%	
Glaucoma stage			
Mild	85.7%	82.6%	0.181[b]
Moderate	14.3%	8.7%	
Advanced	0.0%	8.7%	
Laterality			
OD	48.6%	47.8%	0.584[b]
OS	51.4%	52.2%	
Baseline visual acuity			
20/30 or better	51.4%	52.2%	0.338[b]
20/40 to 20/100	40.0%	47.8%	
20/200 or worse	8.6%	0.0%	

SD standard deviation, *IOP* intraocular pressure
[a] Student's *t* test
[b] Chi-square test

Intraocular Pressure

Figure 2 shows the preoperative and 12-month mean IOP for the iStent and iStent *inject* groups. In iStent eyes, mean IOP reduced from 16.1 ± 3.6 mmHg at baseline to 15.4 ± 2.4 mmHg at 12 months postoperative ($p = 0.201$). In iStent *inject* eyes, mean IOP reduced from 16.2 ± 3.1 mmHg at baseline to 13.1 ± 2.2 mmHg at 12 months postoperative ($p < 0.001$). Mean percent IOP reduction was significantly greater in iStent *inject* eyes (19.1%) than iStent eyes (4.3%) ($p < 0.001$). Even though baseline IOP was similar in the two groups ($p = 0.882$), mean IOP at 12 months was significantly lower in the iStent *inject* group than the iStent group ($p < 0.001$).

Figure 3 depicts the distribution of IOP at 12 months postoperative in each group, which showed a lower IOP range for iStent *inject* than iStent eyes. Correspondingly, a significantly greater proportion of iStent *inject* eyes than iStent eyes achieved IOP < 18 mmHg (100% vs. 80.0% of eyes, respectively; $p = 0.035$), IOP < 15 mmHg (73.9% vs. 34.3% of eyes, respectively; $p = 0.003$), and IOP < 12 mmHg (26.1% vs. 0% of eyes, respectively; $p = 0.002$) at 12 months (Fig. 4).

Medications

Figure 5 shows the mean number of medications from baseline to 12 months for each group. At baseline, the iStent and iStent *inject* groups had a similar mean number of medications (1.8 vs. 1.7, $p = 0.565$). At 12 months postoperative, iStent *inject* eyes reduced medication burden by 94.1% ($p < 0.0001$) and iStent eyes decreased their medication burden by 72.2% ($p < 0.0001$). The percent reduction in medications was significantly greater in iStent *inject* eyes than in iStent eyes ($p = 0.023$). Additionally, iStent *inject* eyes had a significantly lower mean number of medications than iStent eyes at 12 months (0.1 ± 0.2 medications

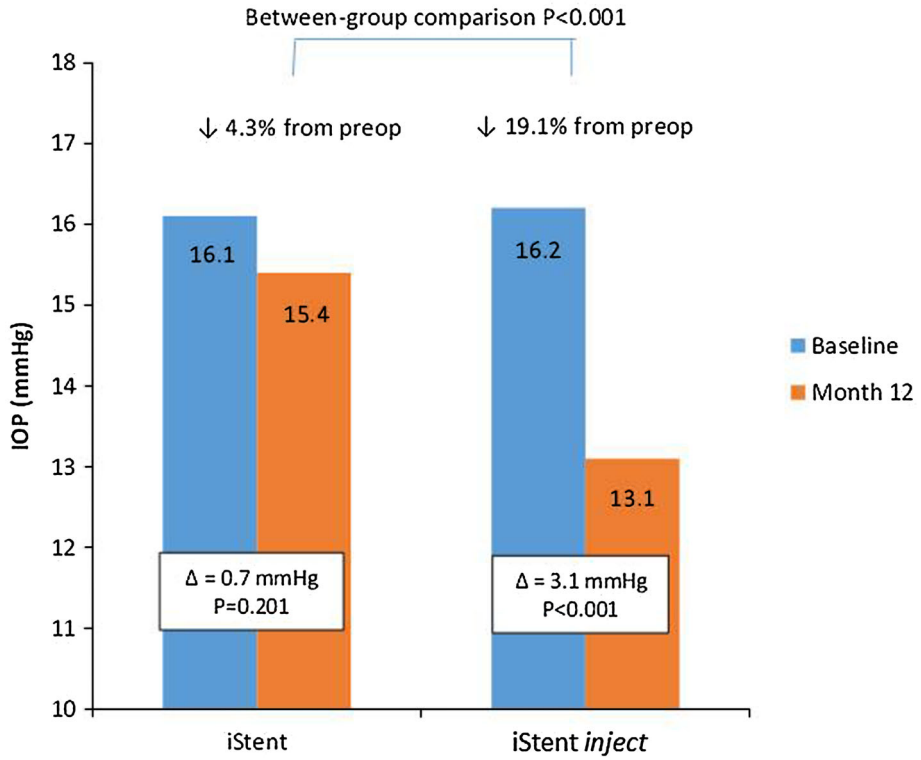

Fig. 2 Baseline and month 12 mean intraocular pressure

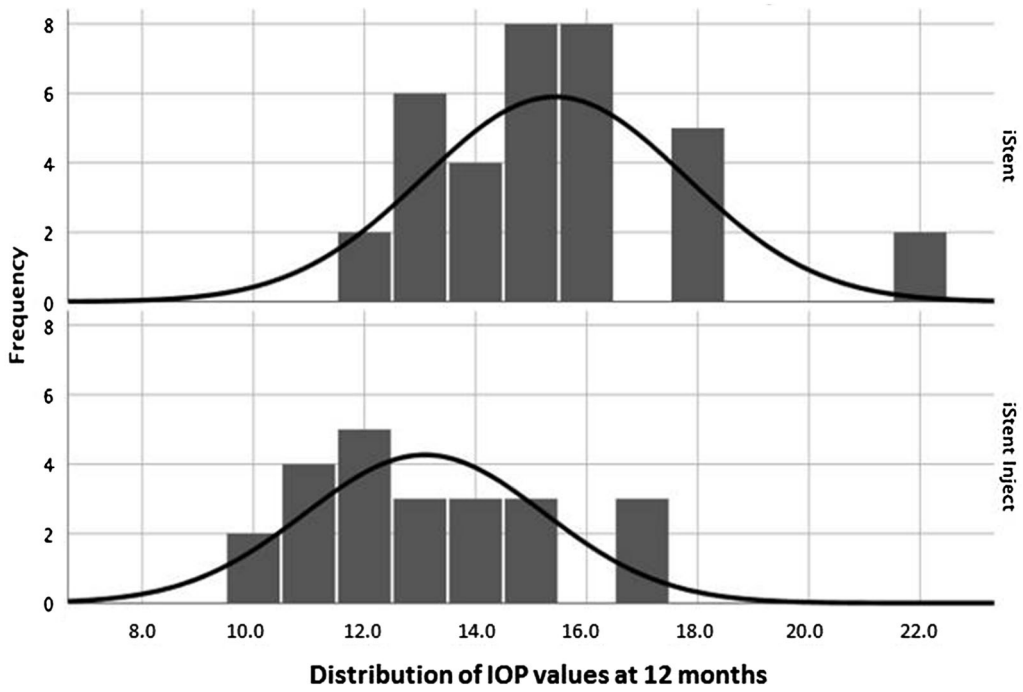

Fig. 3 Intraocular pressure distribution at 12 months postoperative

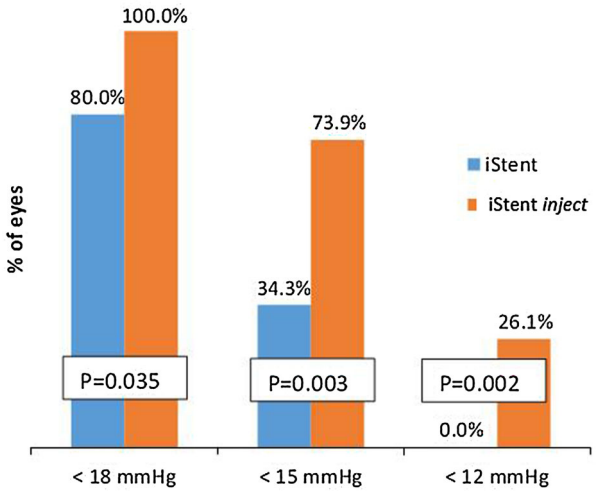

Fig. 4 Proportional analysis of intraocular pressure at 12 months postoperative

vs. 0.5 ± 0.8 medications, respectively; $p = 0.021$).

Figures 6 and 7 show the distributions of medication burden for each group at baseline and 12 months, respectively. At 12 months postoperative, both groups substantially decreased the percentage of eyes on two or more medications and increased the percentage of eyes on zero medications. This shift toward lower medication burden was particularly notable in the iStent *inject* group. Prior to surgery, 62.9% of iStent eyes and 52.1% of iStent *inject* eyes were on two or more medications; meanwhile, 2.9% and 4.3% of eyes, respectively, were medication-free. Twelve months after surgery, only 14.3% of iStent eyes vs. 0% of iStent *inject* eyes were on two or more medications ($p = 0.057$), and 71.4% of iStent eyes vs. 95.7% of iStent *inject* eyes were medication-free ($p = 0.021$). The reductions in number of medications versus baseline were statistically significant at all time points ($p < 0.001$) for both groups.

Safety

Both groups demonstrated a favorable safety profile. A similarly high proportion of patients (87–89%) in each group had no intraoperative adverse events (between-group comparison, $p = 0.336$). There were two intraoperative cases

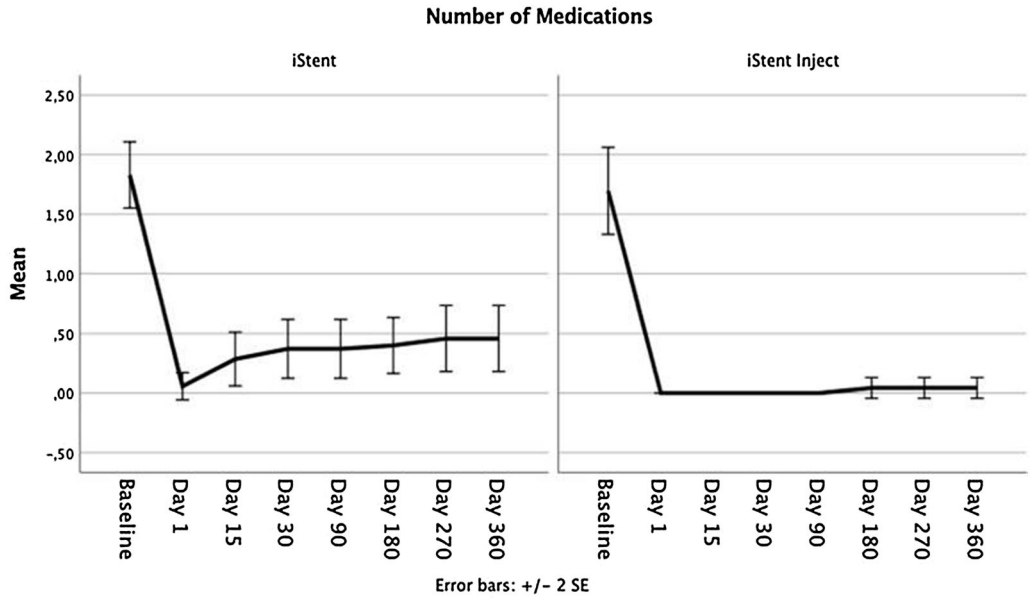

Fig. 5 Mean number of medications from baseline to 12 months postoperative

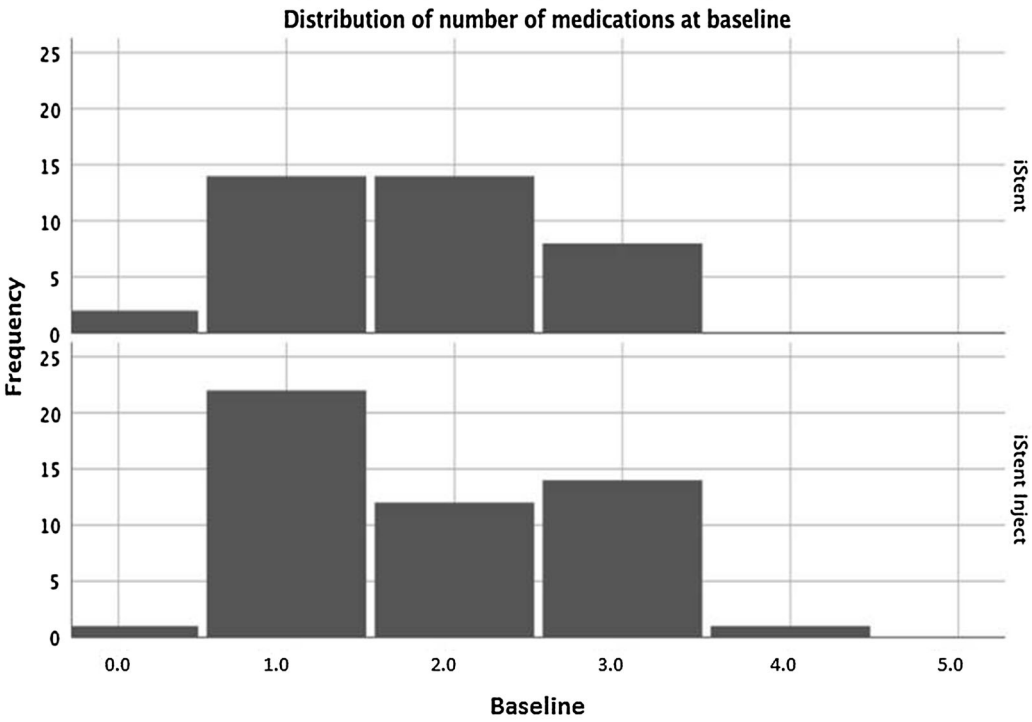

Fig. 6 Baseline distribution of number of medications

of blood reflux in the iStent group that resulted in no associated complications or sequelae. There were two cases of stent misplacement (under- or over-implantation) in iStent eyes and three cases in iStent *inject* eyes, as identified by intraoperative and postoperative gonioscopy.

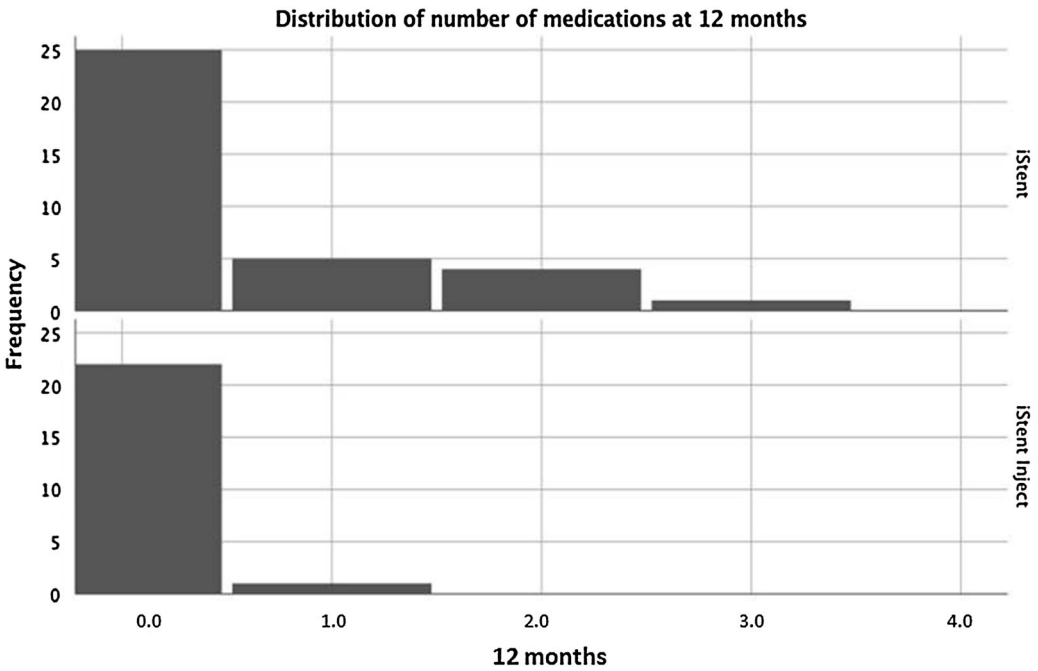

Fig. 7 Month 12 distribution of number of medications

These cases resulted in no sequelae or IOP ramifications, and no additional treatment measures were taken.

During 12 months of follow-up, no adverse events and no secondary glaucoma surgeries occurred in the iStent *inject* group. In the iStent group, one eye had focal peripheral anterior synechiae (PAS) occluding the internal ostia of the iStent at 3 months postoperative. The occlusion was corrected uneventfully with Nd:YAG laser iridotomy and resulted in no sequelae. One iStent eye underwent secondary glaucoma surgery postoperatively (non-penetrating deep sclerectomy, NPDS). This eye had elevated IOP due to systemic steroid use for asthma; no associated stent malfunction was noted. NPDS was completed at 3 months postoperative, and last reported IOP was 14 mmHg on zero medications. No other postoperative adverse events or secondary surgeries occurred throughout follow-up.

Consistent with expectations for phacoemulsification cataract surgery, visual acuity improved in both groups versus baseline. The proportion of iStent eyes with visual acuity of 20/30 or better increased from 51.4% preoperatively to 82.9% at 12 months postoperative ($p = 0.001$); and the proportion of iStent *inject* eyes with 20/30 or better visual acuity increased from 52.2% preoperatively to 95.7% at 12 months postoperative ($p < 0.001$). There were no statistical differences between groups concerning visual acuity proportions at baseline ($p = 0.338$) or at 12 months ($p = 0.147$).

DISCUSSION

This report constitutes one of the first longitudinal comparative datasets of iStent and iStent *inject* with cataract surgery in eyes with glaucoma. In a real-world, single-site, single-surgeon setting, this 12-month series revealed substantial reductions in IOP and medications, with consistently higher efficacy outcomes after iStent *inject* than iStent. These improvements in IOP and medications were accompanied by excellent safety. Given that the dataset included consecutive all-comers in the surgeon's actual patient population, the outcomes may be more generalizable to the broader ophthalmic community of physicians and patients deciding upon glaucoma treatment.

The IOP reduction achieved after iStent *inject* implantation was significantly greater than that of iStent implantation. Trabecular devices act upon the physiologic trabecular outflow pathway and do not eliminate the component of IOP contributed by episcleral venous pressure. As a result, trabecular devices traditionally have been thought to be limited in the level of postoperative IOP they can achieve. Postsurgical IOP in the iStent group was consistent with this expectation, with IOP reducing from 16.1 mmHg at baseline to 15.4 mmHg at 12 months. Meanwhile, iStent *inject* resulted in significantly lower final IOP (13.1 mmHg), suggesting that iStent *inject* may be able to surpass the IOP limitations traditionally ascribed to trabecular devices. Within IDE (investigational device exemption) pivotal trials, iStent *inject* has shown the lowest postoperative IOP (17.1 mmHg) of all trabecular micro-bypass devices [18, 31, 42]. The outcomes in the present study suggest that in real-world usage, postoperative IOP with iStent *inject* could be even lower. Correspondingly, significantly greater proportions of iStent *inject* eyes reached the IOP outcomes (< 18 mmHg, < 15 mmHg, < 12 mmHg) than iStent eyes at 12 months. Given that every 1 mmHg of IOP reduction results in approximately 10% decreased risk of glaucoma progression [3], the additional 2.4 mmHg of IOP lowering afforded by the iStent *inject* device is both statistically significant and clinically meaningful.

Coinciding with IOP reduction, both groups achieved clinically and statistically significant reductions in medications from baseline. The percent reduction in medications was significantly greater in iStent *inject* eyes vs. iStent eyes (94.1% vs. 72.2% reduction, $p = 0.023$). At 12 months postoperative, patients in both groups were able to eliminate an average of 1.6 medications (iStent *inject*) to 1.3 medications (iStent) from their preoperative regimen. Significantly more iStent *inject* eyes (95.7%) than iStent eyes (71.4%) were off medications entirely ($p = 0.021$). The benefits of eliminating medication cannot be overstated, especially for patients who are encumbered by one or multiple topical medications. For example, medications can result in side effects and ocular surface damage [10, 12], and they have costs associated with the drops themselves as well as office visits and caregiving needs [43–45]. Additionally, treatment adherence is widely known to be low, which poses a major obstacle to achieving the consistent IOP reduction needed to minimize risk of optic nerve damage and disease progression. Given that adherence markedly declines with multiple rather than single medications, lower medication burden may allow for improved treatment adherence [8]. With respect to this point, it is noteworthy that 95.7% of iStent *inject* eyes and 71.4% of iStent eyes were off medications entirely at 12 months, and no iStent *inject* eyes and only 14.3% of iStent eyes were on multiple medications. The fact that IOP also declined over the same time period is further demonstration of the overall benefit of implanting the stents.

The observed IOP and medication benefits were consistently greater with iStent *inject* versus iStent implantation in this study, confirming the previously observed comparative advantage of iStent *inject* over iStent in its ability to lower IOP and medications. This advantage is underlain by several key differences in device design between iStent and iStent *inject*. First, the iStent *inject* device consists of an injector preloaded with two stents (versus one stent with the iStent device), facilitating up to 6 clock hours of aqueous outflow by bypassing two separate regions of the trabecular meshwork. Each iStent *inject* stent is designed to carry the 2.5 $\mu L\ min^{-1}$ flow of aqueous humor typically produced by the human eye. Second, multidirectional flow and increased access to collector channels are afforded by the four outlet lumens on each iStent *inject* stent (versus one lumen on the iStent). Third, iStent *inject* stents are smaller and are implanted more directly into Schlemm's canal than the iStent, promoting more straightforward and uncomplicated surgery and possibly softening the learning curve for surgeons new to the procedure.

The design of both devices is supported by studies in aqueous angiography and computational fluid dynamics (CFD), which is considered the most advanced tool to evaluate stent flow and size. CFD modeling showed that

although the iStent and iStent *inject* are microscale devices, each stent had minimal flow resistance and was entirely sufficient to conduct all 2.5 μL min^{-1} of aqueous humor production produced by the human eye [46]. In an in vivo aqueous angiography study, Huang et al. showed significant aqueous outflow improvement after iStent *inject* implantation with cataract surgery [47]. The study's findings showed that formerly dormant outflow areas could be reactivated, allowing access to up to 6 clock hours of collector channels for aqueous egress.

The use of two versus one stent is supported by preclinical and clinical studies demonstrating enhanced efficacy with two trabecular micro-bypass stents compared to a single stent. Within a whole eye perfusion model, Hunter et al. showed 6.0 mmHg of IOP reduction after implantation of a single iStent, and an additional 2.9 mmHg of IOP reduction after implanting a second iStent, for a total IOP reduction of 8.9 mmHg from baseline [46]. Similarly, using an anterior segment perfusion model, Bahler et al. observed an IOP reduction from 21.4 to 12.4 mmHg after implanting one iStent ($p < 0.001$), and a final IOP of 11.9 mmHg in eyes receiving more than one iStent [48]. Subsequently, Bahler et al. used an anterior segment perfusion model to evaluate the second-generation iStent *inject*. Results showed that a single iStent *inject* stent improved outflow facility from 0.16 to 0.38 μL min^{-1} - $mmHg^{-1}$ ($p < 0.03$, $n = 7$), and IOP concurrently decreased from 16.7 to 8.6 mmHg; meanwhile, adding a second iStent *inject* stent further increased outflow facility to 0.78 μL min^{-1} $mmHg^{-1}$ ($n = 2$) [49].

Three clinical studies corroborated these preclinical findings. Belovay et al. and El Wardani et al. assessed two or three iStents in combination with cataract surgery; and Katz et al. completed a prospective randomized trial comparing outcomes after implanting one, two, or three iStents in standalone surgery [30, 50, 51]. These studies consistently showed that the greatest IOP decrease occurred after placement of a single stent, but that additional stents enabled further IOP reductions. This is possibly due to accessing more clock hours of the distal outflow network and thereby increasing the probability of stenting regions of Schlemm's canal that are patent and functional. Together these six preclinical and clinical studies consistently show that although one stent is responsible for the majority of the reduction in IOP and outflow resistance, additional stents produce incrementally greater reductions.

The safety profile of both groups was excellent, consistent with the substantial evidence base showing the favorable safety of these devices [18–40]. Visual acuity remained stable or improved during follow-up, confirming that stent implantation does not diminish any of the visual benefits expected after cataract surgery. There were no cases of the complications seen with filtering surgeries such as endophthalmitis, choroidal detachment or effusion, hypotony, or bleb-related infections or re-needling [14–16].

Of note, the iStent and iStent *inject* devices are made of biocompatible titanium that has a proven excellent safety record. Not surprisingly given this biocompatibility, there were no cases of inflammation (e.g., iritis, uveitis) during the entirety of follow-up in either group in this study. Furthermore, only one eye had PAS, which were focal and readily corrected with Nd:YAG laser with no sequelae. This contrasts with the reported PAS rates of up to 30% observed in trials of other MIGS devices with similar mechanism of action [42, 52–54]. There also were no reports of device dislocation, hypotony, significant hyphema, choroidal detachment, or corneal decompensation such as that cited with some other MIGS devices [55–58].

We acknowledge several limitations in this report. The study was a retrospective, single-site, single-surgeon case series. All cases were drawn consecutively from the surgeon's heterogeneous patient population and thus were not designed to be identical; however, this real-world design may increase the study's relevance to a broader range of clinical settings and patient populations. The present study had a modest number of eyes in each group and documented outcomes through 12 months postoperative, since the iStent and iStent *inject* were relatively recently introduced in Brazil; thus, future possibilities for research may be to

pursue larger sample sizes, longer periods of follow-up, multicenter pooled data, or prospective comparative studies. Since all stent implantations were completed together with cataract surgery, the effect of the stents could not be isolated from that of cataract surgery; however, this simply reflects real-world usage where stents are commonly implanted with cataract surgery. However, since the same surgeon made medication decisions throughout the study, and since medications and IOP are objective numbers, the preoperative values could reasonably be considered as legitimate comparators for postoperative measurements.

CONCLUSIONS

The present study represents a natural evolution from—and confirmation of—the findings of prior preclinical and clinical studies, with side-by-side data on both iStent and iStent *inject* in a real-world clinical setting. The findings show clinically and statistically significant IOP and medication reductions and excellent safety after either iStent or iStent *inject* trabecular micro-bypass implantation together with cataract surgery. Compared to the iStent group, the iStent *inject* group achieved significantly greater reductions in IOP and medications from baseline, had significantly lower 12-month mean IOP and medication burden, and had significantly greater proportions of patients achieving lower IOP levels and elimination of medications.

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Compliance with Ethics Guidelines. All procedures performed were in accordance with the ethical standards of the institutional and/or national research committee (the Institutional Review Board (IRB) of the Paletta Guedes Eye Institute), and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

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

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