Precis: Both nonpenetrating deep sclerectomy (NPDS) and iStent inject are safe and effective when combined with phacoemulsification. The NPDS group presented lower final intraocular pressure (IOP); however, more postoperative intervention and longer recovery time was required.

Aim: The aim of this study was to assess the 1-year efficacy and safety of second-generation trabecular microbypass stent implantation (iStent inject) versus NPDS in association with phacoemulsification (Phaco) for the concomitant surgical treatment of open-angle glaucoma and cataracts.

Materials and Methods: This was a single-center longitudinal retrospective comparative study of eyes treated with Phaco-NPDS, with adjunctive use of collagen matrix implant and mitomycin C (group 1), or Phaco-iStent inject (group 2). The main outcome measures were success rates (absolute success: proportion of eyes with IOP < 18 mm Hg without any glaucoma medication; relative success: proportion of eyes achieving different target IOPs (<18; <15; and <12 mm Hg) with or without medication); mean reduction (%) in IOP and medication use; number of postoperative reinterventions (goniopuncture, needling, and reoperation); and number of complications.

Results: The mean age (y) was 69.3 in group 1 and 72.7 in group 2. Groups 1 (n = 51) and 2 (n = 32) achieved absolute success rates of 74.5% and 81.3%, respectively (P = 0.333). Concerning relative success rates, no significant difference was found for IOP < 18 mm Hg or an IOP < 15 mmHg between the 2 groups. However, significantly more eyes achieved an IOP < 12 mm Hg in the Phaco-NPDS group. The mean percentage of IOP reduction from baseline to the end of follow-up was also statistically higher in group 1 (39.9% vs. 24.5%). Both groups achieved similar results in the mean reduction of medications per eye. No significant complications were found in either group, but patients in group 1 required more postoperative intervention than group 2.

Conclusions: Both techniques are safe and effective for the concomitant surgical treatment of open-angle glaucoma and cataracts and presented comparable relative success rates at different target IOP levels (<18 and <15 mm Hg). A larger proportion of patients in group 1 achieved a target IOP < 12 mm Hg; however, more postoperative intervention was required.

Key Words: cataract, iStent inject, nonpenetrating surgery, open-angle glaucoma, phacoemulsification, trabecular microbypass

In recent years, the ophthalmology field has observed a major evolution in primary open-angle glaucoma (POAG) surgical treatment.1–4 From partial-thickness filtering procedures such as trabeculectomy, safer techniques such as nonpenetrating deep sclerectomy (NPDS) and microinvasive glaucoma surgeries (MIGS) are now available to patients.1–4

NPDS, an ab-externo filtering procedure, promotes an enhancement of aqueous outflow by excising the external trabecular tissues and the inner wall of the Schlemm canal. The remaining trabecular tissue (the uveal and partial corneoscleral trabecular meshwork), prevents penetration of the anterior chamber, avoiding decompression and hypotony-related complications (eg, hypotony maculopathy and choroidal detachment3–5). There is also evidence that mitomycin C (MMC)-enhanced NPDS has comparable efficacy to traditional MMC trabeculectomy, while offering a much safer profile.6

MIGS is a term used to describe a wide range of techniques.7,8 Some of these procedures reduce intraocular pressure (IOP) by creating a new aqueous outflow pathway (subconjunctival or suprachoroidal). Others offer an enhancement of the natural outflow system (Schlemm canal and collector channels). Among the latter, trabecular microbypass devices are used to surgically bypass the trabecular resistance by promoting a patent communication between the anterior chamber and the interior of Schlemm canal.9,10 The iStent inject trabecular microbypass consists of a single-use injector preloaded with 2 titanium stents.11–16 Both filtering and MIGS procedures can be combined with cataract surgery, allowing for the concomitant treatment of both cataracts and POAG.7,17,18

To our knowledge, there has been only 1 comparative study involving trabecular-MIGS and filtering procedures.10 A possible explanation for this is that these types of MIGS and filtering surgeries have different target populations. Although filtering procedures have traditionally been indicated for glaucoma patients with progressive and advanced disease (usually medically uncontrolled patients), MIGS has often been the preferred treatment approach for mild-to-moderate disease (usually medically controlled patients).7,8,20,21 Nevertheless, there are some indications in which both techniques can be considered, such as for medically uncontrolled patients with mild-to-moderate disease and medically controlled patients with advanced disease.
The aim of this study was to evaluate the 1-year efficacy and safety of second-generation trabecular micro-bypass stent implantation (iStent Inject) versus NPDS in association with phacoemulsification for the concomitant surgical treatment of POAG and cataracts.

MATERIALS AND METHODS

This was a comparative retrospective study of consecutive patients submitted to a combined cataract and POAG surgery through one of the following techniques: Phaco-NPDS (group 1) or Phaco-iStent Inject (group 2). All patients underwent surgery at the same center by the same surgeon from January 2017 to December 2018.

The inclusion criteria were as follows:
- Mild-to-moderate [mean deviation (MD) better than −12 dB in Humphrey visual field] POAG, wherein target IOP had not been achieved with medications.
- Advanced (MD equal to or worse than −12 dB) POAG, wherein target IOP had been achieved with medications.
- The presence of clinically significant cataracts.
- The absence of any other ocular findings.
- Twelve months of follow-up after surgery.

Medical records at our clinic are supposed to indicate the individual target IOP for each patient’s eye. We have obtained the information on the target IOP from the medical records.

The exclusion criteria were any other type of glaucoma, including secondary OAG; if both eyes of the same patient were eligible, we randomly selected one of them, through a random number generator; and a lack of data in the records.

Data collection was sequential for both techniques. From January 2017 to December 2017, Phaco-NPDS patients were included, and, from January 2018 to December 2018, Phaco-iStent-inject patients were included. The moment iStent inject was approved in Brazil at the end of 2017, indications of glaucoma surgery for that specific population (described above in the inclusion and exclusion criteria section) gradually migrated from Phaco-NPDS to Phaco-iStent inject.

Besides demographics (age, race, and sex), the following clinical variables were collected from the records: stage of POAG (early, moderate, or advanced, according to Hodapp-Parrish-Anderson criteria); self-reported time from POAG diagnosis; intraoperative and postoperative complications; baseline and postoperative IOPs; baseline and postoperative number of glaucoma medications; baseline and final visual acuity; number of postoperative interventions (lasers, needlings, reoperations, etc.); and time (d) from surgery to return to daily activities. The time required before the patient was able to return to daily activities was obtained from the medical records. In our clinic, physicians usually write down at the medical records the date the patient was informed he/she could resume normal daily activities.

Decision to restart any glaucoma medication was made individually on the basis of target IOP predefined by the physician. No predetermined criteria existed.

We have collected the data looking for specific time-points during the postoperative period: day 1; day 15 (± 5 d); day 30 (± 7 d); day 90 (± 15 d); day 180 (± 30 d); and day 360 (± 30 d).

The main outcome measures were as follows:
- Relative success rates, measured as the proportion of patients achieving predetermined target IOPs (18; 15; and 12 mm Hg) with or without the adjunctive use of glaucoma medications at the end of follow-up (12 mo).
- Absolute success rate, measured as the proportion of patients achieving an IOP <18 mm Hg without any glaucoma medication.
- Percentage of IOP and medication reduction from baseline to the end of follow-up.
- Probability of success (IOP <18 mm Hg with no medications) at 12 months for both groups through a Kaplan-Meier survival analysis.

The surgeon who performed all surgeries was experienced in both techniques. The Phaco-NPDS technique began with corneal traction using 8.0 Vycril (Ethicon Inc., USA), followed by a subconjunctival injection (using a 26-G needle) of 0.2 mg/mL MMC plus 0.1 mL 2% lidocaine. After ~30 seconds, the surgeon created a fornix-based conjunctival Tenon flap, followed by dissection of the superficial scleral flap (5 mm × 5 mm) to one third of the scleral thickness. Dissection of the triangular-shaped deep scleral flap was carried out up to the Schlemm canal. At this point, the surgeon performed a 2.2-mm clear-corneal phacoemulsification at a second site. No conjunctival manipulation was required for cataract surgery. The technique used for phacoemulsification was a standard phaco-chop, followed by intraocular lens implantation without sutures. Thereafter, all viscoelastic material was removed from the anterior chamber. The next step was to resume the NPDS and finish the deep scleral flap. As the dissection progressed anteriorly, it unroofed the Schlemm canal. Sclerectomy of this deep scleral flap was then

| TABLE 1. Comparison of Clinical Variables Between Study Groups |
|---------------------------------------------------------------|
| **Clinical Variables**                                       | **Group 1** (Phaco-NPDS) (n = 51) | **Group 2** (Phaco-iStent Inject) (n = 32) | **Statistical Significance** |
| Age (mean ± SD) (y)                                          | 69.3 ± 9.2                        | 72.7 ± 7.5                                    | 0.082                        |
| Baseline IOP (mean ± SD) (mm Hg)                             | 19.8 ± 6.9                        | 18.4 ± 3.2                                    | 0.293                        |
| Baseline number of medications (mean ± SD)                   | 2.6 ± 0.8                         | 2.4 ± 0.9                                     | 0.250                        |
| Sex (%)                                                      | Male/female 54.9/45.1              | 40.6/59.4                                     | 0.149                        |
| White (%)                                                    | 64.7                              | 75.0                                           | 0.527                        |
| African (%)                                                  | 17.6                              | 15.6                                           |                               |
| American (%)                                                 | 17.6                              | 9.4                                            |                               |
| Mixed (%)                                                    | 17.6                              | 9.4                                            |                               |
| Glaucoma stage (%)                                           | Early 33.3                        | 34.4                                          | 0.365                        |
| Moderate 31.4                                                | 43.8                              |                                               |                               |
| Advanced 35.3                                                | 21.9                              |                                               |                               |
| Time of medication use before surgery (y) (%)                | < 10 80.4                         | 84.4                                          | 0.440                        |
| ≥ 10 19.6                                                    | 15.6                              |                                               |                               |
| Baseline VA—Snellen (%)                                      | 20/30 or better 7.8               | 6.3                                           | 0.339                        |
| 20/40 to 20/100                                              | 86.3                              | 78.1                                          |                               |
| 20/200 or worse                                               | 5.9                               | 15.6                                          |                               |

IOP indicates intraocular pressure; Phaco-NPDS, phacoemulsification nonpenetrating deep sclerectomy; VA, visual acuity.
performed, followed by peeling of the external trabecular membrane with delicate forceps. No sutures were used for repositioning the superficial scleral flap. An Ologen collagen matrix (model 862051) was applied at this point as 2 separate pieces [the surgeon cut a round 12 mm (D) ×1 mm (H) Ologen implant into 2 different-sized pieces under microscopic visualization]. The larger piece was placed under the conjunctival flap and Tenon flap, and the smaller piece was placed under the superficial scleral flap. Tenon flap and the conjunctiva were sutured by separate stitches using 8.0 Vycril.

The Phaco-iStent inject technique was as follows. Standard phacoemulsification with a foldable intraocular lens was first performed. Next, implantation of the trabecular microbypasses was conducted through either the main clear corneal phacoincision (for the right eye) or collateral paracentesis (for the left eye). No additional incisions were necessary for the implantation. The surgeon implanted both devices under direct gonioscopic view in the inferonasal quadrant (1 to 2 clock hours apart), looking for areas with blood reflux within the Schlemm canal or higher pigmented areas in the trabecular meshwork. Accurate positioning of the iStent inject was verified by gonioscopic examination, which was performed both during surgery and at all clinical examinations throughout follow-up.

We used a χ² test for the analysis of categorical variables and Student t test in both independent and paired sample comparisons for the numerical variables with normal distribution. We have tested the normality through the Kolmogorov-Smirnov test. For the analysis of non-normal distribution variables, we have used a nonparametric test (Kruskal-Wallis test). Comparisons of the survival curves were performed through the Mantel-Cox test. Statistical analysis was performed using SPSS software. A P-value of 0.05 was used as the threshold for statistical significance.

All procedures were conducted in accordance with the Declaration of Helsinki, and the study protocol was approved by the Ethics Committee of Santa Casa de Misericordia Hospital. Clinical trial registration was not required, due to the retrospective design of the study.

### RESULTS

The study population comprised 83 eyes from 83 patients (group 1, Phaco-NPDS: 51 eyes; group 2, Phaco-iStent inject: 32 eyes). The mean age (y) was 69.3 and 72.7 for groups 1 and 2, respectively. Table 1 lists the clinical variables of the 2 groups. Groups were homogenous with regard to race, sex, glaucoma stage, time from diagnosis, baseline IOP, baseline visual acuity, and number of preoperative glaucoma medications.

Mean visual field MD index for groups 1 and 2 was, respectively, as follows: −9.53 and −8.74 dB (P=0.339, t test).

### IOP Results

The mean (±SD) baseline IOPs in groups 1 and 2 were 19.8 ± 6.9 and 18.4 ± 3.2 mm Hg (P=0.293, t test), respectively. We observed a statistically significant reduction in IOP (P<0.001, paired t test) at all timepoints during the follow-up to 12 months for both groups.

Table 2 and Figure 1 present the changes in IOPs from baseline to the end of follow-up in groups 1 and 2.

The absolute success rate for an IOP <18 mm Hg was 74.5% in group 1 and 81.3% in group 2 (P=0.333, χ² test).

| Timepoints | Phaco-NPDS (n = 51) | Phaco-iStent Inject (n = 32) | Statistical Significance (Between-group Comparison) |
|------------|---------------------|-----------------------------|---------------------------------------------------|
| Baseline   | 19.8 ± 6.9          | 18.4 ± 3.2                  | 0.293                                              |
| Day 1      | 14.3 ± 7.0*         | 11.9 ± 2.9*                 | 0.064                                              |
| Day 30     | 10.9 ± 2.7*         | 14.5 ± 3.1*                 | <0.001                                             |
| Day 90     | 12.3 ± 3.7*         | 13.2 ± 2.2*                 | 0.192                                              |
| Day 180    | 12.0 ± 4.1*         | 13.3 ± 2.4*                 | 0.057                                              |
| Day 360    | 11.9 ± 3.8*         | 13.9 ± 2.0*                 | 0.005                                              |

*IOP values in both groups achieved a statistically significant reduction compared with baseline values (P<0.001 at all timepoints). IOP indicates intraocular pressure; Phaco-NPDS, phacoemulsification nonpenetrating deep sclerectomy.

**FIGURE 1.** Intraocular pressure change from baseline to the end of follow-up (12 mo). Phaco-NPDS indicates phacoemulsification nonpenetrating deep sclerectomy.
Table 3 lists the relative success rates, and Figure 2 presents the Kaplan-Meier survival curves for both groups. The mean percentage of IOP reduction from baseline to the end of follow-up was 39.9% in group 1 and 24.5% in group 2 ($P=0.023$).

### Medication Burden Reduction

The mean (± SD) number of glaucoma medications per eye at baseline was 2.5 ± 0.8 in group 1 (Phaco-NPDS) and 2.4 ± 0.9 in group 2 (Phaco-iStent inject) ($P=0.250$). At 12 months, the mean (± SD) dropped to 0.2 ± 0.4 and 0.3 ± 0.8 in groups 1 and 2, respectively. Comparisons between the 12-month number and the baseline number of medications achieved statistical significance at all timepoints ($P<0.0001$, paired t test) for both groups. Table 4 and Figure 3 show the change in mean number of medications per eye.

The proportions of eyes at the end of follow-up with no medications in groups 1 (Phaco-NPDS) and 2 (Phaco-iStent inject) were 78.4% and 84.4% ($P=0.356$, $\chi^2$ test), respectively.

### Safety Results

No significant intraoperative complications were observed in either group. Only 1 case of intraoperative significant bleeding was observed in the NPDS group. This specific patient used anticoagulants and could not stop this medication for the ocular surgery, as advised by the cardiologist.

Concerning postoperative complications, a few complications were present in the NPDS group. We observed 1 case of bleb failure, 1 case of temporary bleb leakage (with spontaneous resolution), and 1 case of a shallow anterior chamber. No postoperative complications were observed in the iStent inject group. Transient mild IOP elevation was observed in the iStent inject group around the third and fourth weeks postoperatively, which was identified to be related to a mild steroid-induced response. No glaucoma medication was necessary to treat this IOP spike, and withdrawal of steroid was sufficient to treat it.

We have not observed any intraocular inflammation or any cataract surgery-related complication in both groups.

Postoperative interventions were present only in the NPDS group: bleb needling in 1 case and laser gonipuncture in 25 cases (49%). Mean ± SD and median times for the laser gonipuncture application were 4.5 ± 4.3 and 4 months, respectively. One case developed shallow anterior chamber and clinically significant hypotony (IOP <4 mm Hg) after laser gonipuncture.

### Return to Daily Activities

The mean time to return to daily activities differed between the 2 groups (Fig. 4). Patients in the Phaco-NPDS group returned to their normal daily activities on average after 31.59 (± 4.82) days versus 14.78 (± 2.86) days in the Phaco-iStent inject group ($P<0.001$, $t$ test).

### DISCUSSION

The iStent inject trabecular microbypass stent device aptly demonstrates the 5 fundamental criteria of MIGS surgery, which include a high safety profile, minimal tissue
IOP levels, we noticed that these rates were similar for IOP spectrum.10,25,26 Both NPDS, evaluated in this study, and lower-risk surgical modality on the glaucoma treatment microbypass is widely acknowledged to be a less invasive, trauma, rapid recovery, at least modest efficacy, and a microinvasive (usually ab-interno) approach.7,24 Trabecular microbypass is widely acknowledged to be a less invasive, lower-risk surgical modality on the glaucoma treatment spectrum.10,25,26 Both NPDS, evaluated in this study, and trabeculectomy are filtering procedures, which lie farther along the spectrum of the disease due to their higher risks and remain the standard treatments for more advanced cases.1,3,6,27,28

As expected, iStent inject presented a significant higher final mean IOP versus NPDS (mean IOP, 13.9 vs. 11.9 mm Hg, respectively, at 12 months, \( P = 0.005 \)). Although iStent inject implantation was not expected to produce the same IOP reductions of a filtering surgery, in our study, it produced a comparable efficacy profile if we look into other outcome measures.

Statistically, the same proportion of patients achieved an IOP <18 mm Hg with no medications [absolute success rate: 74.5% (Phaco-NPDS) vs. 81.3% (Phaco-iStent inject), \( P = 0.333 \)]. Comparing the relative success rates at different IOP levels, we noticed that these rates were similar for IOP <18 mm Hg and IOP <15 mm Hg. Both techniques achieved similar results for IOP <15 mm Hg. This is very encouraging, as this target pressure is usually beneficial and sufficient for the great majority of glaucoma patients, including more advanced cases.29–31

However, more patients achieved IOP <12 mm Hg in the Phaco-NPDS group. This is expected because bleb-dependent procedures, such as NPDS, are known to produce lower IOPs. These results are comparable to those found in the literature, further demonstrating the capability of this technique to achieve low target IOPs in a significant proportion of patients.6,18 This is particularly significant and important for eyes with end-stage disease.30

The higher safety profile of iStent inject, along with the lesser need for postoperative interventions and faster return to normal daily life, may outweigh the difference in efficacy for lower target IOPs (<12 mm Hg). This positive benefit-to-risk assessment is particularly applicable to patients with mild-to-moderate glaucoma that does not yet warrant the risks of filtering surgery or NPDS.

Although NPDS is a safer option compared with trabeculectomy, it still can produce intraoperative and postoperative complications.6,32 The presence of a residual membrane prevents abrupt decompression of the eyeball. This helps limit the damaging effects of severe hypotony with the complications known to exist in postoperative follow-up of classic trabeculectomies.3,4,32 The main potential intraoperative complications include perforation of the residual trabecular membrane and significant bleeding. No perforation was reported in this Phaco-NPDS case series, whereas only 1 case of conjunctival/episcleral hemorrhage was observed. The most common postoperative complication after NPDS is IOP elevation due to external filtration blockage (bleb fibrosis) or internal filtration blockage [iris incarceration (peripheral anterior synechiae at the filtration site) and thickening of the residual trabecular tissue].32 The bleb fibrosis rate in our study was relatively low (1/51). This is possibly due to the technique, which included both MMC and collagen implant adjuvants. These adjuvants are known to lower the rate of bleb fibrosis in NPDS.18 Thickening of the residual trabecular tissue is a common occurrence after

### TABLE 4. Number of Medications (Mean ± SD) Change From Baseline to the End of Follow-up

| Timepoints | Phaco-NPDS (Mean ± SD) | Phaco-iStent Inject (Mean ± SD) | Statistical Significance (Between-group Comparison) |
|------------|------------------------|-------------------------------|---------------------------------------------------|
| Baseline   | 2.6 ± 0.8              | 2.4 ± 0.9                     | 0.250                                              |
| Day 1      | 0.0*                   | 0.0*                          | NA                                                 |
| Day 30     | 0.0*                   | 0.2 ± 0.7*                    | 0.044                                              |
| Day 90     | 0.2 ± 0.4*             | 0.3 ± 0.8*                    | 0.201                                              |
| Day 180    | 0.2 ± 0.4*             | 0.3 ± 0.8*                    | 0.463                                              |
| Day 360    | 0.2 ± 0.4*             | 0.3 ± 0.8*                    | 0.463                                              |

*Mean number of medications in both groups achieved a statistically significant reduction compared with baseline values (\( P < 0.001 \) at all timepoints).

NA indicates not applicable; Phaco-NPDS, phacoemulsification non-penetrating deep sclerectomy.

<FIGURE 3. Change in the mean number of medications per eye during follow-up. Phaco-NPDS indicates phacoemulsification non-penetrating deep sclerectomy.”>
NPDS32; treatment commonly involves Nd:YAG laser goniopuncture. Our series showed a significant (49%) prevalence of this postoperative complication. No iris incarceration was observed during the follow-up.

In a wide range of clinical studies, from single-surgeon case series to large multicenter randomized controlled trials, the first-generation iStent and second-generation iStent inject have both demonstrated favorable safety profiles compared with cataract surgery alone.2,33 In accordance with the literature, we observed a very high safety profile in our series. No intraoperative or postoperative complication was observed during the follow-up.

Both techniques had a similar impact on medication burden reduction. From >2.0 glaucoma medications per patient on average during the preoperative period, the mean number of medications per patient dropped to 0.2 in the Phaco-NPDS group and 0.3 in the Phaco-iStent inject group. The great majority of patients became medication-free in both groups (78.4% and 84.4% in Phaco-NPDS and Phaco-iStent inject groups, respectively; \( P = 0.356 \)). These results demonstrate the ability of both techniques to improve patients’ adherence and quality of life by making patients less dependent on the daily use of eye drops and are in accordance with the published literature.

In our study, patients submitting to Phaco-NPDS returned to their daily activities, on average, 1 month after surgery. One great advantage of the combined Phaco-iStent inject technique is the faster recovery from surgery. Compared with Phaco-NPDS, Phaco-iStent patients returned to their normal lives after an average of 15 days (ie, in half the time compared with Phaco-NPDS patients), thus greatly benefitting the patients. Our results are very encouraging. Many patients, for whom a phaco-filtering procedure is the technique of choice, can migrate to a safer and faster recovery technique (Phaco-iStent inject), without totally compromising efficacy (IOP control and medication burden reduction).

Our study had several limitations, including its retrospective design and a relatively small number of cases. Our small sample size could affect the power to identify small differences between treatment groups; hence, conclusions should be taken with caution. A prospective randomized clinical trial comparing these 2 techniques will be needed to confirm our findings. Moreover, glaucoma is a chronic disease, and hence longer follow-ups will be necessary to ensure the ability of both techniques to maintain the results and avoid disease progression.

CONCLUSIONS
Both techniques, Phaco-iStent and Phaco-NPDS, are safe and effective for the concomitant surgical treatment of POAG and cataracts. Patients in the Phaco-iStent inject group experienced a shorter recovery time. Both groups presented comparable relative success rates at different target IOP levels (<18 and <15 mm Hg). A larger proportion of patients in the Phaco-NPDS group achieved a target IOP <12 mm Hg; however, more postoperative intervention was necessary with this procedure.

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