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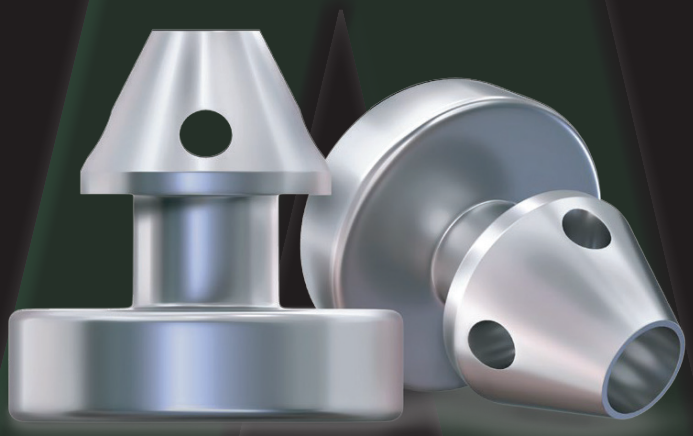

TRABECULAR MICRO-BYPASS: LIFE IN THE REAL WORLD

Why real-world data is important when treating glaucoma patients.

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Sayeh Pourjavan, MD

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Why Real-World Data Is Important for Glaucoma

WATCH NOW

Data helps drive treatment decisions, while patient care is best when individualized.

BY ALBERT S. KHOURI, MD

Glaucoma surgeons face the common conundrum of deciding what is the best treatment for the patient sitting before us. Established practice patterns for the treatment of mild, moderate, and severe open-angle glaucoma can be helpful, but the decision largely comes down to individualizing patient care. This requires a combination of referring to randomized controlled trials (RCTs), relying on real-world data, and drawing from personal experience and comfort to counsel patients toward the best procedure for their condition.

RCTs provide the highest level of evidence, but trial protocols vary greatly in the content and quality of the design. Additionally, many trials to date have focused on mild to moderate open-angle glaucoma, and large RCTs have not been devised to compare different MIGS procedures. The relevancy of RCTs to our daily practice, and especially to our individual patients, can be minimal. One must consider the minutia of the clinical trial design, such as patient characteristics, inclusion and exclusion criteria, and how the study was executed, to determine the value in its application in real-life medicine. One must also look at treatment protocols and reporting for baseline IOP, IOP with and without medications, IOP with and without washout, IOP reduction, and absolute and qualified success definitions to determine the value and the accuracy of the reported findings.

A MODIFIED RCT

Let's look at one example of an RCT that was modified mid-study so that it could provide better guidance for real-world practice.

The original protocol of the COMPARE trial included washout at the 12-month follow-up visit to allow direct comparison of the reduction in IOP associated with two MIGS devices, iStent® (Glaukos) and Hydrus (Alcon), without the additional effects of concomitant medications.[1] In approximately 20% of the first 40 eyes to reach 12-month follow-up, however, the trial investigators were probably not willing to adhere to the washout because of persistent IOP elevation despite application of maximally tolerated medical therapy. As a result, the study protocol was modified, and the 12-month washout requirement was eliminated.[1]

Thereafter, medications were added or removed at the discretion of the unmasked investigators. The Kaplan Meier event-free survival curve defined treatment success as patients who were medication-free, so reintroduction of medications by the unmasked investigators was a fundamental limitation of the study.

ADVANTAGES AND DISADVANTAGES OF REAL-WORLD DATA

I believe we must look beyond RCTs to real-world data to guide an individual patient's care. For MIGS, most of the data we have comes from investigator-initiated trials (IITs). Some of this real-world data boasts advantages over RCTs, such as longer follow-up periods; more diverse populations, glaucoma types, and severity; and lower associated cost to conduct.

On the other hand, IITs are heterogenous in design. They can be nonrandomized, prospective, or retrospective cohorts. They can also be a single case series. Additionally, many IITs tend to have a smaller sample size and shorter follow-up compared to RCTs, and they are typically single site initiatives.

There are some longer-term IITs, however, including the Longer-Term Real-World Clinical Data for MIGS from iStent (Glaukos), that go out up to 8 years and include a diverse patient population, including patients with more severe glaucoma.[2] After 5-year follow-up, Hengerer and colleagues showed that patients experienced significant IOP reductions after iStent *inject*® alone and combined with phacoemulsification (Figure 1).

I was recently involved in an IIT that looked at the iStent® in Black patients, a population that typically has more severe glaucoma.[3] We found that the combination

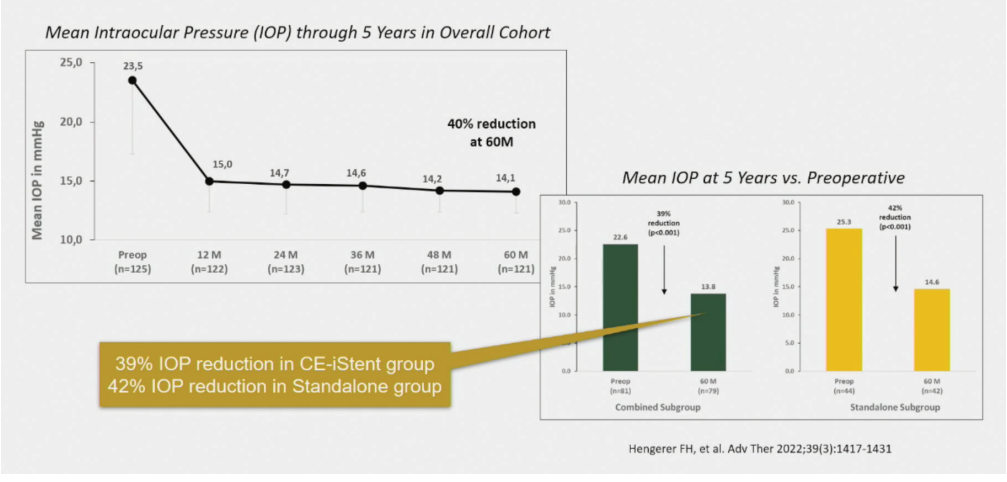

Figure 1. Five-year reduction in IOP after combined phacoemulsification and iStent *inject*® and after iStent *inject*® alone.

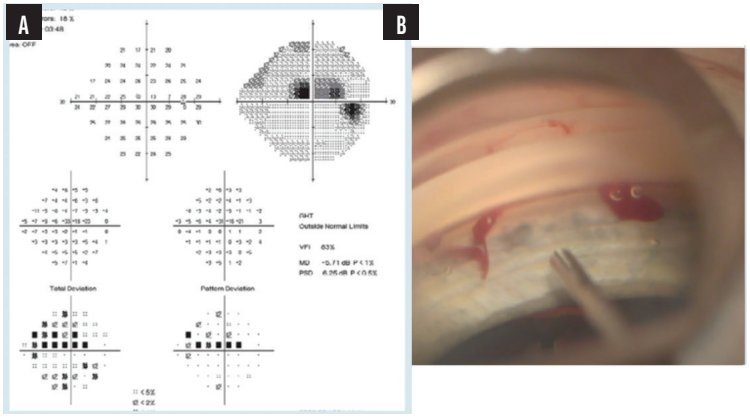

Figure 2. Preoperative assessment (A) and the intraoperative intervention with the iStent *inject*® (B).

of phacoemulsification with the iStent® worked well in patients with higher IOPs (>25 mm Hg) but not as well when the pressures were in the mid-teens. This lesson is easily applicable in clinical practice.

Evidence-based medicine should guide treatment options. When you're sitting with a patient, however, individualized care is best. In this article, I highlight two cases in which I referred to real-world data while also using my own clinical judgement to decide what was the best treatment choice for the patient's current condition and future prognosis.

CASE NO. 1

A 23-year-old woman who just learned she had glaucoma presented for an evaluation. She was in her first trimester of pregnancy and did not want to use any medications that could jeopardize the baby's health. Most glaucoma medications, however, are not studied in the context of pregnancy. On OCT, she had a healthy optic nerve and a preserved retinal nerve fiber layer, but her IOP was 32 mm Hg.

According to the AAO guidelines for glaucoma disease severity, this patient would fall under the category of early glaucoma. She had a fully preserved field and very early retinal nerve fiber layer changes.

Her pressures got worse (40s and 50s mm Hg). I performed a trabeculectomy under topical anesthesia without Mitomycin C. The patient did fairly well in the end. The trab survived the patient's pregnancy, and her pressures came down after she delivered the baby.

This case highlights how guidelines do not always apply in real-world medicine. The patient had mild glaucoma by structure and function testing standards, yet she needed incisional surgery.

CASE NO. 2

A 59-year-old lawyer presented with glaucoma that was progressing despite treatment with three IOP-lowering drops. He had loss of inferior retinal nerve fiber layer and a superior defect about 3 years before the examination (Figure 2). He also had a cataract and expressed a desire to return to work quickly. Again, according to AAO guidelines, the patient could fall under the category of moderate or perhaps severe glaucoma, depending on his visual field. His field defect, however, was within 5° of fixation.

Typically, patients like this with severe glaucoma are not included in RCTs. I elected to perform combined phacoemulsification and iStent *inject*®, and the patient fared really well. He was able to go back to work quickly, as he wished, and his pressures were around 13 mm Hg postoperatively on a prostaglandin analog.

> "As we individualize patient care, we should heavily rely on patient-based factors, like expectations for recovery, threshold for surgical risks, and quality of life considerations, in addition to evidence-based literature considerations, such as the stage of the disease, how fast it is progressing and how far the patient is from their target IOP."

CONCLUSION

In patients like those described in this article, it is best to individualize their care rather than rely on RCTs to guide treatment decisions. Even though RCTs provide a strong level of evidence, they are not always applicable for patients sitting in the examination chair in front of us.

Glaucoma surgeons have many choices now. Typically, MIGS interventions fall somewhere in the middle of the treatment paradigm, between earlier interventions like drops and lasers and more involved options for severe disease such as incisional surgery. As we individualize patient care, we should heavily rely on patient-based factors, like expectations for recovery, threshold for surgical risks, and quality of life considerations, in addition to evidence-based literature considerations, such as the stage of the disease, how fast it is progressing and how far the patient is from their target IOP. RCTs provide strong evidence to guide treatment, but real-world data are pooled from a more diverse patient population with varying severity, which can be more useful for individualizing your approach to surgery. ■

1. Khouri AS. Re: Ahmed IIK, Fea A, Au L, et al. A prospective randomized trial comparing Hydrus and iStent microinvasive glaucoma surgery implants for standalone treatment of open-angle glaucoma: the COMPARE Study. *Ophthalmology*. 2020;127(4):e23-e24.
2. Hengerer FH, Auffarth GU, Conrad-Hengerer I. iStentinject trabecular micro-bypass with or without cataract surgery yields sustained 5-year glaucoma control. *Adv Ther*. 2022;39(3):1417-1431.
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What is Real-World Data Teaching Us?

The iStent *inject*® W is improving patients' quality of life.

BY SAYEH POURJAVAN, MD

The use of the iStent® technologies (Glaukos) is supported by a large body of clinical evidence, including more than 200 peer-reviewed articles with up to 8 years of follow-up, 17 ongoing sponsored studies, and real-world data from more than 1 million stents implanted worldwide. This article outlines two studies that support the independent and long-term effect of the iStent® micro-bypass device on IOP and medication burden.

STUDY NO. 1

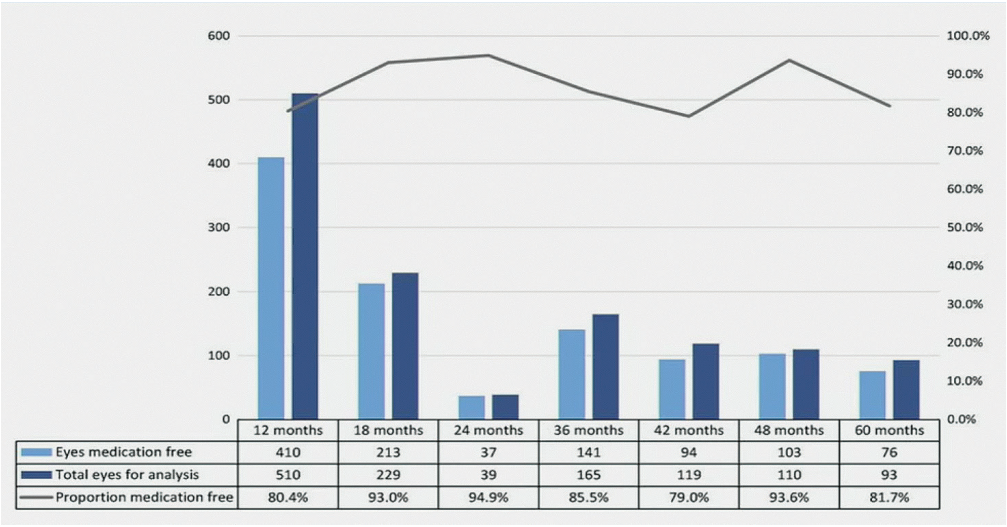
Healey PR, Clement CI, Kerr NM, Tilden D, Aghajanian L. Standalone iStent trabecular micro-bypass glaucoma surgery: a systematic review and meta-analysis. J Glaucoma. *2021;30(7):606-620.*

Study design. Healey et al pooled data from 778 eyes across 13 studies (four randomized controlled trials and nine nonrandomized or single-arm studies) to determine the effects of standalone trabecular micro-bypass glaucoma surgery with iStent® devices in patients with open-angle glaucoma. The follow-up was a minimum of 6 months and up to 60 months. The study population was heterogeneous; some studies concentrated on newly diagnosed patients while others included those who were uncontrolled with one or two medications, those who were not controlled with two or three medications, and those who needed incisional surgery.

Results. There was a 31.1% weighted mean reduction in IOP at 6 to 12 months. For the studies that reported longer-term outcomes, the weighted mean reduction in IOP was 30.4% between 36 and 48 months and 32.9% at 60 months. When the results were pooled across all studies at 6 to 12 months and 36 to 60 months after iStent® surgery, the weighted mean reduction in IOP from baseline was 7.01 mm Hg (95% confidence interval) and 6.59 mm Hg (95% confidence interval), respectively. Between 6 and 18 months post-implantation, the medication burden was reduced by about 1 medication and by 1.2 medications between 36 and 60 months (Figure 1). Of the 510 who were available for follow-up at 12 months, about 410 were free of medication. Of the 93 patients available at 60 months, 76 (81%) were free of medication.

The adverse events were minimal but included progression of preexisting cataract (which is not surprising given the age of the study population) and loss of BCVA. The rates, however, were no different compared to those reported in comparative medical therapy study arms. Only 4.5% required cataract surgery, and 2.6 eyes required a secondary glaucoma intervention in the form of a filtering procedure. Personally, I don't consider that to be a complication because the iStent® is not designed to replace a trabeculectomy.

Conclusion. The study by Healey et al demonstrates the independent effect of the iStent® on IOP and medication burden over a 5-year follow-up period. Between 80% and 95% of patients were free of medication after receiving the iStent®, and there was a better mean reduction in IOP (7.3 mm Hg) between 6 and 12 months when two iStent® were implanted.



	12 months	18 months	24 months	36 months	42 months	48 months	60 months
Eyes medication free	410	213	37	141	94	103	76
Total eyes for analysis	510	229	39	165	119	110	93
Proportion medication free	80.4%	93.0%	94.9%	85.5%	79.0%	93.6%	81.7%

Figure 1. Number and proportion of eyes medication/additional medication free by timepoint. Each study may contribute to multiple timepoints as reported in source document. Three studies did not report the proportion of eyes medication free at any timepoint.

STUDY NO. 2

Nichani P, Popovic M, Schlenker MB, Park J, Ahmed IIK. Microinvasive glaucoma surgery: a review of 3476 eyes. Ophthalmology. *doi.org/10.1016/j.survophthal.2020.09.005*

Study design. Nichani and colleagues performed a review of 3,476 eyes across 20 randomized clinical trials that were published in English and were peer-reviewed. Observational studies were included with the target follow-up of at least 1 year. The study compared combined phacoemulsification and MIGS versus phacoemulsification

> "In my hands, the iStent *inject*® W is a straightforward procedure, has a short learning curve and less complications, and fewer postoperative visits compared to a trabeculectomy."

alone. It also compared various MIGS procedures and MIGS versus topical medication.

Results. For the purposes of this article, the results presented here are for the phaco-iStent® cohorts relative to control and studies comparing standalone iStent *inject*® procedure to topical medications. In that population, the IOP reduction was greater when an iStent® was implanted in combination with cataract surgery. Additionally, patients achieved a greater reduction in the number of medications required postoperatively. In comparing the placement of one, two, and three iStent® devices, the washed-out IOP decreased in a dose-response fashion. In other words, the more iStent® that were placed, the lower the pressure. The effect was less pronounced when two and three iStent® devices were compared.

The study also showed insignificant endothelial cell loss at 24 months when phacoemulsification was combined with the iStent® compared to phacoemulsification alone (10.4% vs 9.5%). This study did not have any follow-up beyond 2 years.

An additional surgical intervention was required in 3.3% of patients who underwent phacoemulsification plus iStent® and 5.5% of patients who underwent standalone phacoemulsification at a mean follow-up of 21.6 months.

Conclusion. The iStent® technologies are not intended to replace more invasive glaucoma treatment methods but rather to address the gap between invasive and more conservative glaucoma treatments. The study by Nichani et al showed that iStent® is more cost effective in treating glaucoma than topical medication per quality-adjusted life year versus phacoemulsification alone.

PERSONAL EXPERIENCE

When we looked at our results from 132 eyes of 100 patients who received at least one iStent® device, patients achieved a significant decrease in IOP—between 25% to 30%, or 5 to 6 mm Hg—and medication use by one class at 6 months postoperative (P <.001) (Table).

We have been using the iStent *inject*® W since November 2021. We have implanted this new-generation device in 58 patients as a combined phacoemulsification/iStent® procedure and 12 as a standalone iStent *inject*® W procedure in those who had previous phacoemulsification but were poorly controlled with three to four topical medications.

I like to use the iStent *inject*® W whenever the target IOP cannot be obtained with multiple medications, in order to delay the need for trabeculectomy. In older patients who are still phakic but require a trabeculectomy, I remove the cataract first to achieve a better postoperative result and place an iStent *inject*® W as a patch to win time. This procedure is straightforward laser trabeculoplasty, which is especially useful for the backlog of patients we have experienced as a result of COVID-19. I will also place an iStent *inject*® W after when patients have a cataract to be sure that the IOP will not become elevated. For patients who have Alzheimer's disease and frequently forget to put in their glaucoma drops, I combine phacoemulsification with the iStent *inject*® W.

TABLE. RESULTS WITH THE ISTENT *INJECT*® AT DR. POURJAVAN'S PRACTICE.

Outcome	Mean IOP	# of Meds
Pre-op	20.9±5.6	2±1.5
1 Day	15.7±3.8	NA
7 Days	21.9±7.8	0
1 Month	17.2±4.2	0.8±1.1
3 Months	16.1±3.0	0.98±1.3
6 Months	15.3±3.3	1.1±1.3

ADVANTAGES

In my hands, the iStent *inject*® W is a straightforward procedure, has a short learning curve and less complications, and fewer postoperative visits compared to a trabeculectomy. iStent® is a trabecular micro-bypass and not a subconjunctival procedure. There is no bleb formation and therefore no bleb maintenance is needed. I can perform a trabeculectomy or place a tube under a naive conjunctiva.

The major advantage of the iStent *inject*® W is that it can delay the need for a more invasive procedure, bridging the waiting time from cataract surgery to trabeculectomy.

CONCLUSION

The quality of life of our patients should always be top of mind. In addition, IOP-lowering drops can be costly, are difficult to use for elderly patients, and are not environmentally friendly (plastic thrown away in single-dose drops). In properly selected patients, the latter is the best option to improve patients' quality of life by decreasing IOP and reducing their medication burden. ■

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- Financial disclosure: None

How to Use Trabecular Micro-Bypass Procedures in the Real World

The iStent *inject*® W technology fits into my busy clinical practice.

ROBERT PETRARCA, MD (RES), FRCOPHTH, MBBS, MCOPTOM, BSC(HONS)

Our aim as eye surgeons is to save sight and make our patients happier. I consider the iStent *inject*® W (Glaukos) for any patient with a cataract and glaucoma. Generally, patients are very happy with the procedure because not only does their vision improve, but the burden of glaucoma therapy on their daily life is reduced. The result is a better quality of life.

INDICATIONS

The iStent *inject*® W restores the conventional pathway for natural outflow of aqueous humor. When two stents are used, not only is the trabecular meshwork bypassed, but the stents help maintain the aqueous outflow pump and increase the size of Schlemm's canal and the collector channel recruitment up to 90°.

The iStent *inject*® W is indicated for patients with mild to moderate primary open-angle glaucoma and is intended for use in combination with cataract surgery. I typically like to use it in patients who are on one or more glaucoma medications with controlled or uncontrolled IOP. Additionally, however, the iStent *inject*® W can be a good choice for those who have a poor ocular surface because it can help reduce the burden of treatment. These patients are often on multiple drops, their eyes are red, and their conjunctiva is inflamed. It's also great for patients who are not good at physically putting drops in their eyes or keep forgetting to put them in (see Case Study). This includes a large proportion of the patients we see in a standard glaucoma clinic.

There is a small but important cohort of patients in whom the iStent *inject*® W should not be used. Especially during the learning curve, this includes patients with advanced, angle-closure, synechiae angle-closure (especially nasal), neovascular, and secondary traumatic glaucoma. It also should be avoided in patients with uveitis, those who have a history of trabeculectomy surgery, in the presence of ciliary body masses and abnormalities, and those who have difficulty rotating their neck.

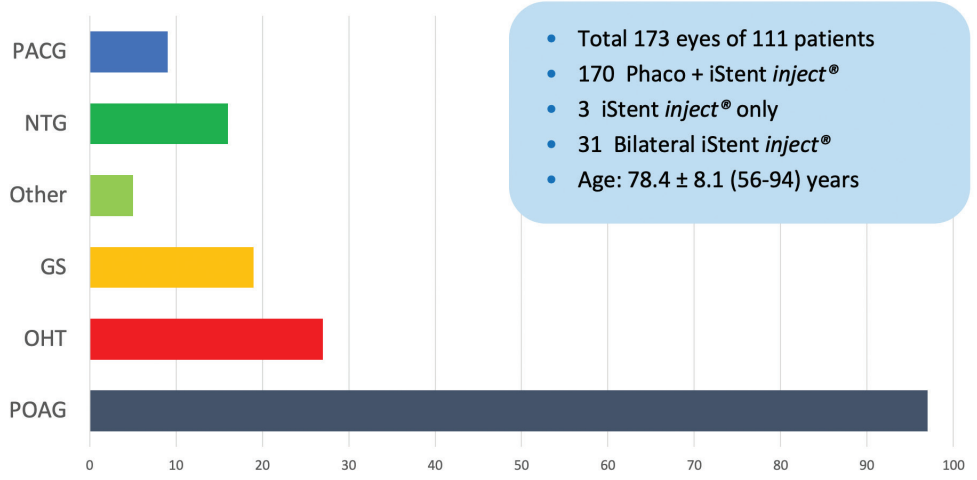

Figure 1. The study at Dr. Petrarca's clinic included a wide range of diagnoses. [Abbreviations: PACG, primary angle-closure glaucoma; NTG, normal tension glaucoma; GS, glaucoma suspect; OHT, ocular hypertension; POAG, primary open-angle glaucoma]

MANAGING A BUSY CLINIC

With any surgical intervention, we want to minimize the risk for hypotony, macular edema, and a flat anterior chamber—all common complications after more complex surgeries. The iStent® procedure, however, requires very little postoperative interventions.[1] It produces a predictable result and a quiet, stable eye with a low complication rate.[2-4] This is important, especially when you are managing a busy clinic. In my clinic, we usually do about 100 iStent® procedures per year. This year, however, we're already up to 80.

I generally do the iStent® before the cataract surgery procedure because I feel it gives me the best view, especially in eyes with a pale trabecular meshwork, and is the most repeatable way of doing the procedure in my hands. It also gives me two tries at injecting the stents. If I feel like it can't be achieved at the beginning of the combined procedure, then I can re-attempt after cataract surgery is completed.

Postoperatively, patients take tobramycin and dexamethasone ophthalmic suspension (Tobradex, Novartis) four times a day for 3 weeks while continuing their glaucoma medications. Previously, patients were seen at 1 week. At that visit, we stopped their medication use and they returned at

CASE STUDY

About 2 years ago, an 83-year-old man presented with glaucoma (IOP 26 mm Hg OD and 28 mm Hg OS) and cataract. He suffered from arthritis and struggled to put drops in by himself. He also had Parkinson disease and severe dry eye disease. Oftentimes, his daughters had to put the drops in his eyes for him.

The patient underwent uncomplicated bilateral cataract surgery and iStent *inject*® procedures. After only 4 weeks, all eye drop medications were discontinued, his vison improved, and his IOP was 14 mm Hg OD and 15mm Hg OS. He was delighted with the results from a single minimally invasive procedure that not only improved his sight but also achieved a medication-free, controlled IOP and improved his ocular comfort and quality of life.

3 or 4 weeks for evaluation. That, however, increased the burden on patients to return to the hospital and on our staff who were seeing these patients.

Now, patients return 3 to 6 weeks after their surgery. At that point, we do gonioscopy, check their pressure, and start tapering the glaucoma eyedrops down—usually the twice a day medication first and then any once a day medication, and then none.

Patients return for subsequent follow-up between months 2 and 3 and are seen by a nurse technician. Visual field is repeated at that visit. When patients are off of their drops, they transition to tech-led virtual clinics, where they have pressures measured. This new protocol works well for us, and it reduces the burden of treatment for our patients.

PERSONAL EXPERIENCE

We recently compared our results to the 2-year pivotal trial results[5] and assessed the mean change in IOP and the number of IOP-lowering medications our patients were on after the iStent *inject*® procedure. A total of 173 eyes of 111 patients with at least 1-month follow-up were included; there were 170 phacoemulsification plus iStent *inject*® procedures and three iStent *inject*® only. Thirty-one procedures were performed bilaterally. The mean age of patients was 78.4 ± 8.1 years (range, 56–94). The diagnosis for all patients is shown in Figure 1, and the changes in IOP and the number of eye drops patients were on postoperatively are shown in Figure 2.

Our results were in line with the results from the pivotal study. In our study, 83% of eyes experienced a 20% reduction in IOP at 1 month and 92% at 3 months. Up to 12 months, 75% of patients maintained the 20% reduction. The mean IOP reduction was 5 mm Hg. Additionally, 49% of patients experienced a reduction in the mean number of topical medications they were on.

In our group, therefore, patients achieved a reduction in their IOPs and halved their medication simply due to a safe, repeatable procedure performed at the same time as their cataract surgery.

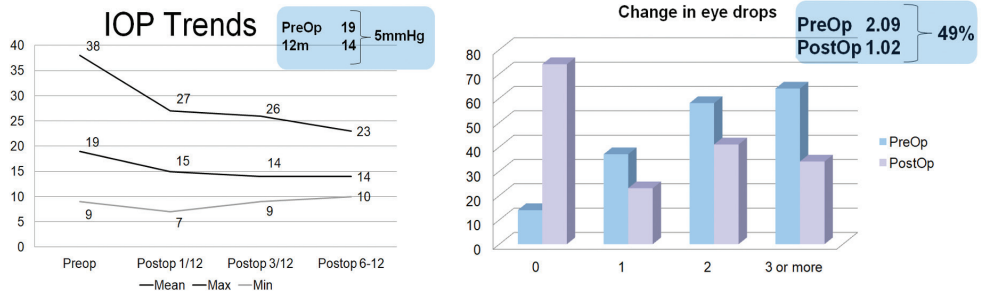

Figure 2. Changes in IOP and the number of eye drops patients were on after iStent *inject*® surgery.

WHAT IS THE FUTURE?

Our waiting rooms are back to pre-COVID-19 levels, if not higher. An increasing number of patients have high IOPs who can benefit from a combined procedure such as phacoemulsification and iStent *inject*® W. Sometimes, these patients are diverted away from glaucoma clinics and undergo cataract surgery without any intervention for their elevated IOP at another location. These are missed opportunities for MIGS procedures in this environment.

Of all the MIGS procedures that are available, I believe the iStent *inject*® W is one of the best options for surgeons who operate in high-volume cataract surgery settings. Current literature supports my personal experience that the procedure can be performed safely without a need for increased follow-up care, there is a short learning curve, and patients can achieve a good lowering of IOP in a very elegant and safe procedure with minimal risk and follow-up.

Today, it's important for us to treat glaucoma patients earlier in the disease state. Our patients love the combination of improved vision and the reduced burden of glaucoma with the iStent *inject*® W procedure, and we love the minimum impact it can have on our workflow with good, safe clinical results. ■

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iStent *inject*® W IMPORTANT SAFETY INFORMATION

INDICATION FOR USE: The iStent inject® W, is intended to reduce intraocular pressure safely and effectively in patients diagnosed with primary open-angle glaucoma, pseudo-exfoliative glaucoma or pigmentary glaucoma. The iStent inject® W, can deliver two (2) stents on a single pass, through a single incision. The implant is designed to stent open a passage through the trabecular meshwork to allow for an increase in the facility of outflow and a subsequent reduction in intraocular pressure. The device is safe and effective when implanted in combination with cataract surgery in those subjects who require intraocular pressure reduction and/or would benefit from glaucoma medication reduction. The device may also be implanted in patients who continue to have elevated intraocular pressure despite prior treatment with glaucoma medications and conventional glaucoma surgery. **CONTRAINDICATIONS:** The iStent inject® W System is contraindicated under the following circumstances or conditions: • In eyes with primary angle closure glaucoma, or secondary angle-closure glaucoma, including neovascular glaucoma, because the device would not be expected to work in such situations. • In patients with retrobulbar tumor, thyroid eye disease, Sturge-Weber Syndrome or any other type of condition that may cause elevated episcleral venous pressure. **WARNINGS/ PRECAUTIONS:** • For prescription use only. • This device has not been studied in patients with uveitic glaucoma. • Do not use the device if the Tyvek® lid has been opened or the packaging appears damaged. In such cases, the sterility of the device may be compromised. • Due to the sharpness of certain injector components (i.e. the insertion sleeve and trocar), care should be exercised to grasp the injector body. Dispose of device in a sharps container. • iStent inject® W is MR-Conditional; see MRI Information below. • Physician training is required prior to use of the iStent inject® W System. • Do not re-use the stent(s) or injector, as this may result in infection and/or intraocular inflammation, as well as occurrence of potential postoperative adverse events as shown below under "Potential Complications." • There are no known compatibility issues with the iStent inject® W and other intraoperative devices. (e.g., viscoelastics) or glaucoma medications. • Unused product & packaging may be disposed of in accordance with facility procedures. Implanted medical devices and contaminated products must be disposed of as medical waste. • The surgeon should monitor the patient postoperatively for proper maintenance of intraocular pressure. If intraocular pressure is not adequately maintained after surgery, the surgeon should consider an appropriate treatment regimen to reduce intraocular pressure. • Patients should be informed that placement of the stents, without concomitant cataract surgery in phakic patients, can enhance the formation or progression of cataract. **ADVERSE EVENTS:** Please refer to Directions For Use for additional adverse event information. CAUTION: Please reference the Directions For Use labelling for a complete list of contraindications, warnings and adverse events.

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