iStent: Trabecular Micro-Bypass Stent

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3.1 Device Design

The iStent (or iStent Trabecular Micro-Bypass Stent) (Glaukos Corporation, San Clemente, USA) has become a popular device within the realm of minimally invasive glaucoma surgery (MIGS). These procedures are known to have a higher safety profile and a more rapid recovery time in comparison to more invasive filtering surgery. MIGS procedures have demonstrated the ability to both reduce IOP and a patient's need for medications, a significant benefit considering concerns regarding compliance rates among glaucoma patients [1]. Unlike many other surgical interventions for glaucoma, iStent implantation does not diminish the superlative visual and refractive outcomes inherent to modern phacoemulsification. As with many MIGS procedures, stent placement is minimally traumatic to the target tissue and spares the conjunctiva via an *ab interno* approach.

The iStent was developed by Glaukos (Glaukos Corporation, San Clemente, CA, USA) with the first implantation in the United States performed in 2005 [2]. The stent is designed to fit into and remain within Schlemm's canal. Made from non-ferromagnetic titanium, it consists of an inlet (or "snorkel") connected at a 40° angle to the implanted portion. The stent itself is then attached to the tip of a 26-gauge disposable insertion instrument, which has been sterilized by gamma radiation (Fig. 3.1a, b). The inserter tubing contains four-finger extensions which grasp the stent. A pointed end of the device facilitates entry into the canal and the direction of this point corresponds to the designation of a right or left-handed model (GTS100R and GTS100L, respectively). Depending on the preference of the surgeon, both "right" and "left" iStents have been developed to ease implantation. The segment residing within the canal includes a half cylinder opening, which combined with heparin coating, helps to prevent blockage or fibrosis. Three retention arches

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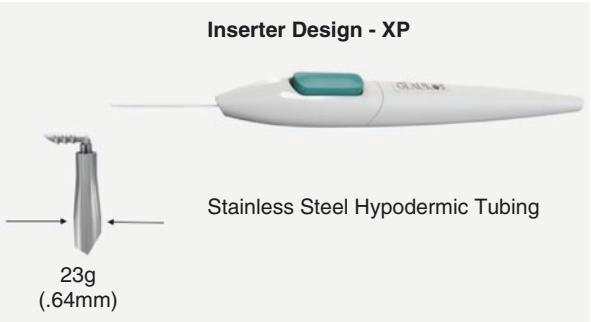

Fig. 3.1 The direction of the pointed end with the inserter held upright (button on the top) designates right or left-handed models. (Copyright Glaukos Corporation, San Clemente, CA, USA; reproduced with permission)

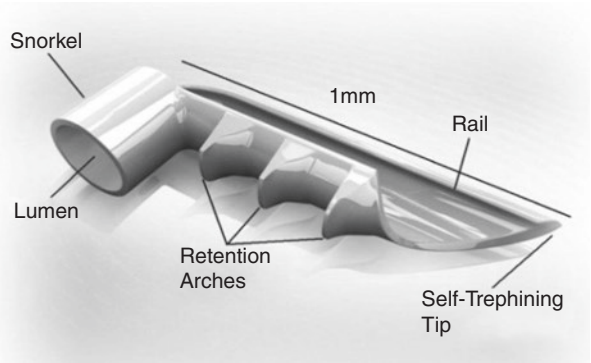

Fig. 3.2 Implanted in the trabecular meshwork, the stent allows aqueous humor to flow into Schlemm's canal. (Copyright Glaukos Corporation, San Clemente, CA, USA; reproduced with permission)

help to ensure that the device will be held in place within the canal. The implant is 1.0 mm in length, 0.33 mm in height, and with a weight of 60 μg. The snorkel has a length of 0.25 mm and bore diameter of 120 μm [3] (Fig. 3.2).

The iStent *inject* system (Glaukos Corporation, San Clemente, CA, USA), a second-generation device or G2, consists of an apical head connected to a narrow thorax that is attached to a wider flange. Currently, the smallest medical implant approved for use in the human body, the implant is 360 μm in length and with a diameter of 230 μm (Fig. 3.3a, b). The central inlet and outlet lumen has a diameter of 80 μm. The head is inserted directly into the canal without the necessity to adjust the angle for implantation. It resides within the canal and contains four inlets for fluid passage, each with a diameter of 50 μm. The 23-gauge stainless steel injector contains two stents for implantation in the nasal angle, at a distance of approximately 30–60° (Fig. 3.4). The iStent *inject* was approved for use in Europe in 2006, and FDA approval in the United States was obtained in June 2018.

The iStent works at the level of the trabecular meshwork (TM). Research regarding the physiology of primary open-angle glaucoma (POAG) has demonstrated that the diseased juxtacanalicular meshwork is the primary site of reduced outflow facility resulting from increased outflow resistance [4]. Implantation of the device allows

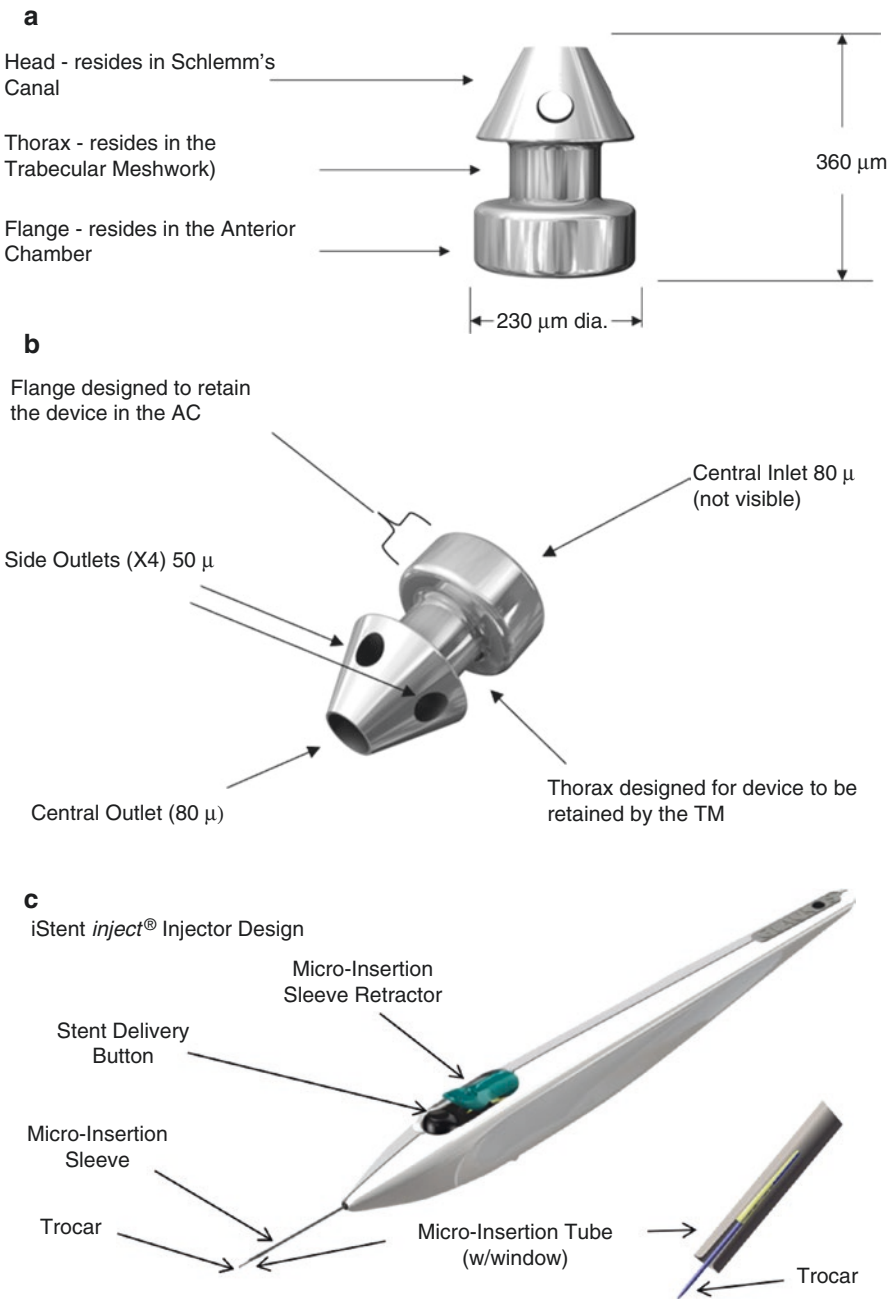

Fig. 3.3 (**a**, **b**) The iStent *inject* is the smallest known medical implant used in the human body. (**c**) The trochar of the injector system pierces the trabecular meshwork, allowing the distal portion of the stent to be injected into Schlemm's canal. (Copyright Glaukos Corporation, San Clemente, CA, USA; reproduced with permission)

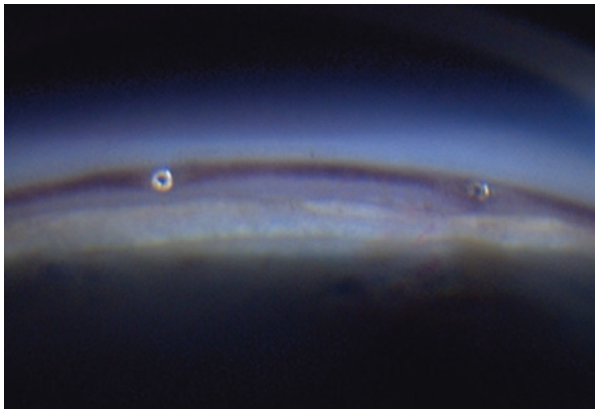

Fig. 3.4 The iStent *inject* system allows for implantation of two preloaded trabecular micro-bypass stents with a single entry. (Copyright Thomas Samuelson, MD; reproduced with permission)

for aqueous to bypass the increased TM resistance to outflow and provides a direct pathway into Schlemm's canal and the subsequent collector channels. The postoperative IOP would not be expected to fall below the episcleral venous pressure (EVP), which has been reported in different studies to range between 7.6 and 9.1 mmHg [5–7] and may be elevated in some glaucoma patients [8]. This is a limitation in the treatment of patients with very low target IOP; however, a benefit in the avoidance of hypotonous sequelae.

Zhou et al. demonstrated the effectiveness of trabecular bypass on outflow facility and IOP [9]. A series of equations explored this relationship and demonstrated that in normal healthy eyes, the outflow facility increases by 13 and 26% in the presence of a unidirectional and bidirectional bypass, respectively. The IOP could be reduced to physiologic levels with outflow facility enhancement. Bahler et al. looked at the effect of a trabecular meshwork bypass on IOP in cultured human anterior segments [10]. A single stent placed into Schlemm's canal provided the greatest change in pressure (21.4 ± 3.8 mmHg to 12.4 ± 4.2, $P < 0.001$) with the addition of more stents providing further lowering of pressure, but to a lesser degree.

Similarly, Bahler et al. also addressed the influences of the iStent *inject* on the outflow facility of cultured human anterior segments [11]. Outflow facility was shown to increase and IOP to decrease with a single stent placement. An additional increase in outflow facility was demonstrated with the placement of a second stent.

3.2 Patient Selection

In 2012, the FDA approved the iStent for use in combination with cataract extraction for patients with mild-to-moderate open-angle glaucoma who were using between 1 and 3 ocular hypotensive medications. The stent is currently approved in Europe as a stand-alone procedure or for use in combined cataract/MIGS procedures.

Ideal candidates are those with stable and well-controlled or modestly uncontrolled disease. Patients demonstrating rapid progression or extreme elevation of IOP on their current medication regimen may require more aggressive surgical

intervention such as filtration surgery. Optimal patients typically need pressure lowering, but not to an extreme level. In addition to improving IOP, another goal is to reduce the dependency on topical medication, but not necessarily advance the aggressiveness of treatment.

Patients with a very shallow anterior chamber with peripheral anterior synechiae are typically avoided, as implantation requires access to Schlemm's Canal. Although the angle will be deeper once the native lens has been removed, implantation in shallow anterior chambers can be more difficult with an increased risk of iris or endothelial damage. Secondary glaucomas related to elevated episcleral venous pressure are less ideal, as successful outcomes require an otherwise functional outflow system. Patients with neovascular glaucoma are contraindicated because of both the increased bleeding risk and reduced function of the outflow system [12].

As the surgeon is first developing their implantation skills and becoming more comfortable with the procedure, it may be of benefit to select patients who would do well with cataract surgery alone. These patients will still likely do well postoperatively should implantation be unsuccessful. Other favorable traits for initial cases might include highly cooperative individuals with at least moderate pigmentation of the TM and easily identifiable angle structures. If a surgeon favors right or left eyes for phacoemulsification, he or she is likely to favor such eyes for initial iStent cases as well.

3.3 Surgical Technique

Proficiency with intraoperative gonioscopy is imperative to success with iStent implantation. For surgeons who do not perform gonioscopy often, it is useful to examine patients in clinic to better familiarize oneself with the angle anatomy. Practicing intraoperative gonioscopy during routine cataract cases can also be of benefit prior to implanting the first stent. Gently touching the anterior meshwork with a viscoelastic cannula can help one become more comfortable with the hand positioning.

Upon completion of cataract surgery and implantation of the IOL, injection of a miotic helps to pull the iris away from the angle and insertion of viscoelastic material will aid in maintaining the anterior chamber. For initial cases, it is desirable to remove all viscoelastic from the retropupillary space and capsular bag before the pupil is constricted. Once more experience is achieved, many surgeons will choose to wait until the iStent has been successfully implanted before the viscoelastic is removed and the miotic instilled. The patient's head and the operating microscope are rotated 30–40° in opposite directions to facilitate a gonioscopic view of the angle. The surgical gonioprism is placed on the cornea with a coupling solution (goniosol, viscoelastic) and the angle is viewed under high magnification. Care to avoid pressure on the eye with the goniolens is important, as resultant corneal striae will impede the view. Likewise, the surgeon should not place pressure on the wound with the insertion trochar to avoid expressing viscoelastic from the eye. Once a clear view of the trabecular meshwork is achieved, the applicator is inserted into the

anterior chamber through the clear corneal incision and advanced across the anterior chamber toward the nasal angle. As mentioned previously, there are two different designs designating the direction of the pointed end. The intent of the unique iStent design is that after implantation, the body of the stent points toward the inferior angle such that right stents are used in right eyes and left stents are used in left eyes (Fig. 3.5). Evidence that right or left orientation makes any clinical difference, however, is lacking. As such, most surgeons believe that right- and left-hand models are interchangeable (i.e., right and left iStents can be used in both right and left eyes) depending on what feels more comfortable (forehand or backhand) in the dominant hand of the surgeon.

The anterior 1/3 of the trabecular meshwork is approached at a 15° angle and is perforated by the tip and advanced into the canal. By slightly adjusting the angle after perforation (lowering the heel and raising the toe), the stent will slide into the canal more easily. A "landing strip" technique has recently been described to help guide implantation. Zheng et al. suggested using a 25-guage microvitreoretinal blade to bisect the trabecular meshwork for less than 1 clock hour, thus creating a guide for assistance stent placement [13]. Once securely positioned with the ridges of stent covered by meshwork tissue, the device is released by pushing the button on the applicator. Subtle posterior pressure and relaxing of the hand will ensure a stable release.

After release, the iStent should appear to be well seated within the canal. The device will be viewed running parallel to the iris plane (Fig. 3.6a, b). The applicator tip is used to gently push the inlet to verify it has memory (i.e., with minimal displacement, it will return to the original position). After successful placement, viscoelastic material should be thoroughly removed at the conclusion of the case.

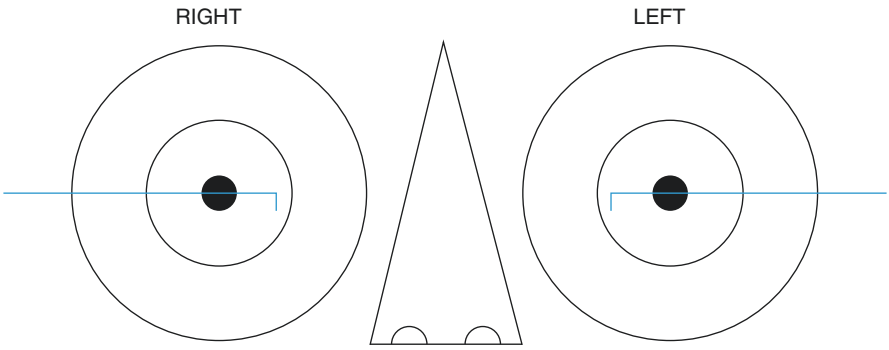

Fig. 3.5 The intent of the unique iStent design is that after implantation, the body of the stent points toward the inferior angle such that right stents are used in right eyes and left stents are used in the left eyes. Evidence that right or left orientation makes any clinical difference is lacking and most surgeons now believe that right- and left-hand models are interchangeable. (Copyright Glaukos Corporation, San Clemente, CA, USA; reproduced with permission)

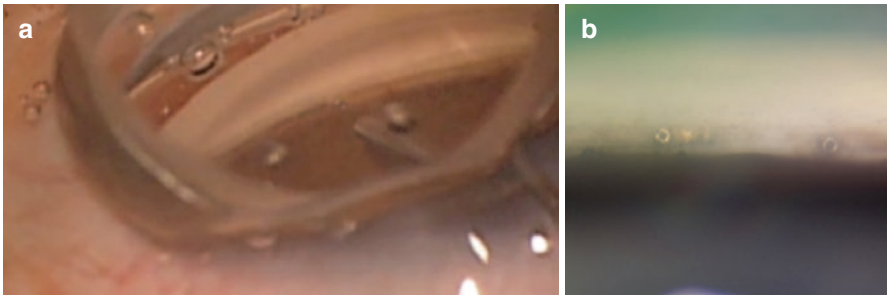

Fig. 3.6 (**a**) With successful implantion, the iStent is viewed running parallel to the iris plane with retention arches covered by trabecular meshwork tissue (Copyright Thomas Samuelson, MD; reproduced with permission). (**b**) Gonioscopy photograph of two iStents showing superficial placement of the left stent as evidenced by visible retention arches. The right stent is well placed in Schlemm's canal and the retention arches are obscured by the pigmented trabecular meshwork. (Copyright Chelvin Sng, FRCSEd; reproduced with permission)

3.3.1 Avoiding Complications and Surgical Pearls

Advantages of the iStent procedure include sparing of the conjunctiva and avoidance of the long-term complications and short-term risks associated with trabeculectomy and tube shunt surgery. More specifically, issues of hypotony are avoided because episcleral backpressure remains.

With any surgical procedure, however, adverse events can occur. The larger studies involving the iStent have not demonstrated any significant added risk in comparison to cataract surgery alone. Publications from the iStent Study User Group at both 12 and 24 months showed the overall incidence of adverse events and long-term safety profile was similar between cataract surgery alone and cataract surgery with iStent implantation. Unanticipated adverse device effects were not seen [14, 15].

Now with several years of use and data, there have been a few case reports published describing isolated complications. Sandhu et al. reported the first documented case of delayed-onset and recurrent hyphema after iStent placement [16]. Two episodes of spontaneous hyphema were seen within a 19-month postoperative period. There were no associations with anticoagulants, stent malposition, or angle abnormalities, and the episodes were thought to be related to ocular pressure from sleeping position that was reduced upon waking. Regarding implantation, Mantravadi et al. reported a case of inadvertent implantation of an iStent into the supracilliary space [17]. An iridodialysis cleft was created at the time of attempted stent repositioning. The stent was no longer visible intraoperatively and was subsequently identified in the supracilliary space via ultrasound biomicroscopy. No adverse sequelae were identified related to the malposition.

Although the overall risks and adverse events seen postoperatively with iStent placement are similar to cataract surgery alone, there are some intraoperative

complexities that may be encountered and steps that can be taken to ensure a successful implantation.

When viewing the angle gonioscopically at the time of stent placement, Schlemm's canal is often highlighted by blood within. This is a benefit in regard to canal identification, but can also impede the view as blood is released after perforation of the trabecular meshwork. If the angle anatomy becomes obscured, irrigation and aspiration may be utilized to clear the blood or additional viscoelastic may push it out of the way. Blood visualized flowing out of the snorkel after insertion is a good but somewhat inconsistent sign, indicating correct positioning within the canal (Fig. 3.7) Quite often blood reflux is not seen until after viscoelastic removal prior to re-pressurization of the eye. Similarly, transient blanching of the episcleral vessels has been proposed as means to confirm accurate stent placement and may be a prognostic indicator (Fig. 3.8a, b). Fellman et al. first described this phenomenon in patients undergoing combined phacoemulsification–trabectome surgery and believed the episcleral venous fluid wave signifies intraoperative structural patency of the conventional outflow system [18]. They were subsequently able to demonstrate a diffuse venous wave resulted in lower IOP, fewer glaucoma

Fig. 3.7 Blood visualized exiting the snorkel of the device can be an indicator of accurate placement. (Copyright Thomas Samuelson, MD; reproduced with permission)

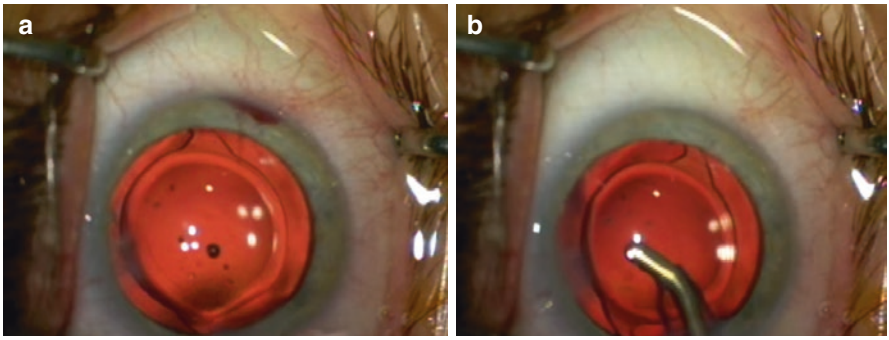

Fig. 3.8 (**a**, **b**) Episcleral vasculature before and after successful iStent placement. The episcleral venous wave demonstrates a structurally intact collector channel system. (Copyright Christine Larsen, MD; reproduced with permission)

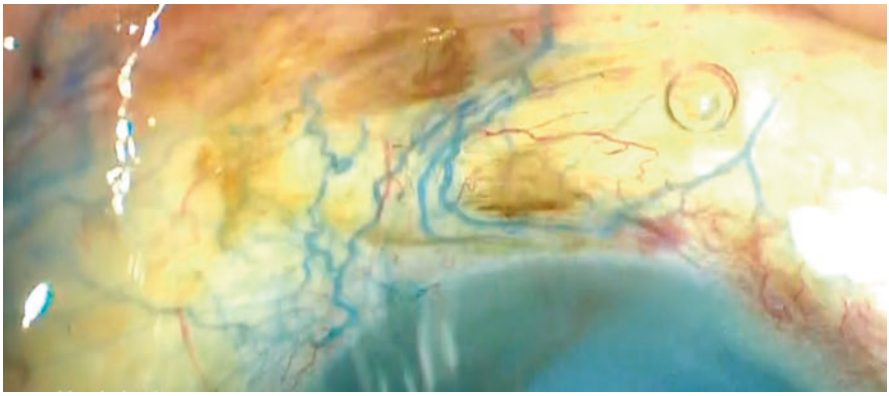

Fig. 3.9 Injection of trypan blue dye in the anterior chamber clearly delineates the aqueous veins in an eye with two well-placed iStent Trabecular Micro-Bypass Stents. (Copyright Chelvin Sng, FRCSEd; reproduced with permission)

medications, and lower requirement for additional surgery in 68 eyes of a similar patient population [19]. Similarly, trypan blue dye (Vision Blue, DORC International) can be used to confirm correct stent placement by allowing the delineation of aqueous veins in blue (Fig. 3.9). This finding has led to the idea of targeted placement. Identification of larger episcleral veins at the beginning of surgery may allow the surgeon to preferentially position the iStent at this location. The same idea is employed under gonioscopic view of the angle. Areas of increased pigmentation or blood within the canal may signify proximity to a collector channel [20] and would thus be an ideal target for iStent placement. Unfortunately, no method exists to evaluate the patency and capacity of collector channels before deciding to proceed with canal surgery. There is also no current mechanism to modulate wound healing in the canal, which can be a detriment to the surgical success of MIGS procedures. The second-generation device, iStent *inject* obviates the need for intelligent placement to some extent by virtue of the fact that more than one stent is placed increasing the likelihood of reaching collector channels.

As discussed earlier, avoidance of patients with shallow anterior chambers can help prevent issues with endothelial damage or iris root tears. Should these occur, the stent can still be safely inserted, however, the patient may require more intensive postoperative care should transient corneal edema or hyphema result.

Another important precaution relates to the re-grasping maneuver should the iStent need repositioning. While the stent can be readily re-grasped by the inserter, care must be exercised to be certain that the re-grasping prongs do not accidentally grasp the iris along with the stent. Should this occur, an iridodialysis or iris trauma could result.

After intraocular lens placement, viscoelastic should be completely removed from both the anterior chamber and posterior to the iris and IOL. Successful evacuation of all viscoelastic is the most important final step in preventing early postoperative IOP spikes. After the instillation of a miotic, the amount of viscoelastic

reintroduced into the anterior chamber should be enough to provide stability and adequate visualization of the canal without resulting in pressure on the meshwork. After stent placement, the viscoelastic is again thoroughly removed. Some surgeons may elect to place the iStent prior to phacoemulsification. One advantage of this strategy is that viscoelastic management subsequently proceeds as per usual for standard cataract surgery. In addition, the view through the cornea may be clearer prior to cataract removal.

3.3.2 Postoperative Management

Open-angle glaucoma patients are more susceptible to intraocular pressure elevation after surgery regardless of whether cataract surgery is performed alone or in combination with iStent placement. In addition to an early postoperative pressure increase related to retained viscoelastic, these patients are also at increased risk of experiencing a steroid response. It may be beneficial to taper steroids more rapidly. The supplemental benefit of a nonsteroidal anti-inflammatory agent often allows earlier discontinuation of steroidal agents.

It will typically take about 6–8 weeks from the surgery date to reach a new steady state for intraocular pressure. Glaucoma medications may be discontinued on a case-by-case basis. Lower risk eyes and those with a lower medication burden (i.e., 1–2 topical medications) may be able to have all glaucoma treatment withdrawn. For those requiring two or more medications or a higher risk patient, medications should be discontinued more cautiously and in a stepwise fashion.

Other potentially encountered issues in the postoperative period include the presence of a hyphema, with possible occlusion of the stent with blood, or occlusion by iris tissue (Fig. 3.10). Treatment of a hyphema in this case is no different than the normal standard of care. Should the stent become blocked with iris tissue, neodymium:YAG laser or argon laser can be utilized to successfully clear the blockage should IOP become uncontrolled [14, 21].

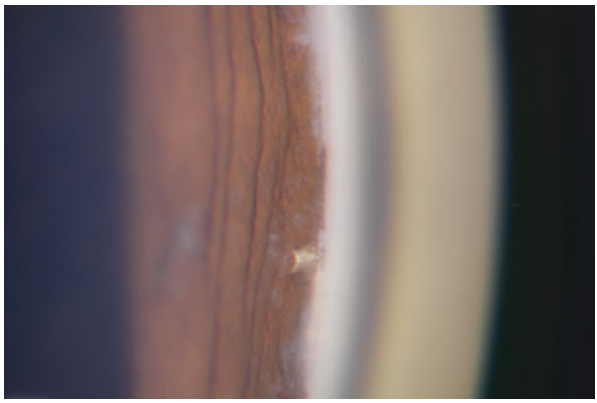

Fig. 3.10 Gonioscopy photograph showing complete iStent occlusion with iris in an eye with angle-closure disease. (Copyright Chelvin Sng, FRCSEd; reproduced with permission)

3.4 Safety, Efficacy, and Clinical Results

3.4.1 iStent Trabecular Micro-Bypass Stent

The US iStent Study Group performed a large comparative study in POAG patients already undergoing planned cataract surgery to compare the effect between cataract removal alone and cataract removal in combination with iStent placement [14]. Prior to this study, several pilot studies had been performed demonstrating the effectiveness of iStent implantation at lowering IOP.

The initial results of the iStent Study Group, the largest study to date, were published in 2011 [14]. The study involved 239 patients with 116 patients receiving the stent. Patients involved in the study were those with mild–moderate glaucoma who had an unmedicated IOP between 22 and 36 mmHg. The primary efficacy measure was defined as unmedicated IOP ≤21 mmHg at 1 year and was seen in 72% of treatment eyes versus 50% of controls. A secondary outcome was unmedicated IOP reduction ≥20% at 1 year and was seen in 66% of treatment eyes versus 48% of controls. Approximately half as many patients in the iStent group were using topical drops compared to the cataract only group at 1 year, suggesting that the iStent may delay or eliminate the need for drops after cataract surgery (a mean reduction in medications of 1.4 for iStent group and 1.0 for cataract only group).

The incidence of adverse events seen with cataract surgery plus iStent placement versus cataract surgery alone was similar in the iStent Study Group. No unanticipated adverse device effects were seen. The goal of improved vision was achieved in ≥95% of subjects for both groups.

A subsequent paper published by the iStent Study Group looked at the same end points at 24 months [15]. It found that the proportion of patients with an IOP of <21 mmHg without medication was significantly higher in the stent group. The mean IOP was stable between the 1 and 2 year end points in the stent group, however, was slightly increased in the control group (17.0 ± 3.1 vs. 17.8 ± 3.3). The total number of hypotensive medications was shown to be significantly less in the stent group at 12 months. This finding was additionally maintained at 24 months, however, was no longer statistically significant. It should be noted that the original study was only powered to detect a difference out to 1 year. Again, postoperative complications and adverse events were similar between groups at 24 months (Table 3.1).

Several publications have since demonstrated similar findings in terms of iStent efficacy and safety profile [22–24]. A summary of the randomized controlled trials and case series to date is provided in Table 3.2. The most common complication across all studies was stent obstruction or malposition, which in general did not result in any adverse sequelae.

3.4.2 iStent *inject*

Fea et al. conducted a randomized, prospective, multicenter evaluation which suggested that treatment with two iStent *inject* devices is comparable to medical

Table 3.1 Postoperative ocular complications reported in the iStent User Group at 24 months

Complication	iStent group (n = 116)	Control group (n = 117)
Anticipated early postoperative event[a]	20 (17.2%)	22 (18.8%)
Posterior capsule opacification	7 (6%)	12 (10.3%)
Elevated IOP	4 (3.4%)	5 (4.3%)
Elevated IOP requiring oral or IV medications or surgery	1 (0.9%)	3 (2.6%)
Stent obstruction	5 (4.3%)	–
Blur or visual disturbance	4 (3.4%)	8 (6.8%)
Stent malposition	3 (2.6%)	–
Iritis	1 (0.9%)	6 (5.1%)
Conjunctival irritation from hypotensive medication	1 (0.9%)	3 (2.6%)
Disk hemorrhage	1 (0.9%)	3 (2.6%)

Abbreviations: *IOP* intraocular pressure
Data from Craven et al. J Cataract Refract Surg. 2012;38:1339–1345
[a]Corneal edema, anterior chamber cell, corneal abrasion, discomfort, subconjunctival hemorrhage, blurred vision, floaters

Table 3.2 Clinical studies involving single iStent placement in combination with phacoemulsification

Study	Design	n	Follow-up (months)	IOP reduction mmHg (treatment)	IOP reduction mmHg (control)	Medication reduction (treatment)	Medication reduction (control)
Fea [38]	RCT	12	15	3 (17%)	1 (9%)	1.6 (80%)	0.6 (32%)
Samuelson et al. [14]	RCT	111	12	8 (33%)	8 (33%)	1.4 (87%)	1.0 (73%)
Craven et al. [15]	RCT	116	24	8 (33%)	7 (28%)	1.3 (81%)	1.0 (67%)
Spiegel et al. [39]	NRS	48	12	4 (18%)	–	1.2 (75%)	–
Arriola-Villalobos et al. [40]	NRS	19	60	3 (16%)	–	0.5 (36%)	–
Vandewalle et al. [41]	CS	10	12	4 (19%)	–	1.0 (37%)	–
Patel et al. [42]	CS	40	6	4 (21%)	–	1.7 (74%)	–
Neuhann [43]	NRS	62	36	9.2 (36%)	–	1.5 (83%)	–
Ferguson et al. [44]	CS	350	24	3.96 (20.7%)	–	0.58 (49%)	–
Seibold et al. [45]	CS	64	12	1.5 (10.2%)	–	0.4 (22%)	–

Note: The value under medication reduction refers to the decrease in the mean number of hypotensive agents, followed by the mean percent reduction from baseline
Abbreviations: *RCT* randomized clinical trial, *CS* case series, *NRS* non-randomized study, *IOP* intraocular pressure

therapy and may be of benefit in reducing the medication burden [25]. Similarly, the Synergy Trial was a multicenter prospective, post-market, unmasked study conducted in Europe consisting of 99 patients with OAG who underwent implantation of two GTS400 stents as a stand-alone procedure [26]. Patients were on at least two topical ocular hypotensive medications and required additional IOP lowering. Eighty-one percent of subjects achieved IOP ≤ 18 mmHg with either a single medication or no medication. Reduction from preoperative medication burden was seen in 86.9% of patients. A summary of completed studies to date is included within Table 3.3.

The iStent *inject* Study Group conducted a large prospective, randomized, single-masked, concurrently controlled, multicenter clinical trial to compare the effect between combined cataract surgery and iStent *inject* implantation with cataract surgery alone [27]. After uncomplicated phacoemulsification, eyes with mild-to-moderate POAG and unmedicated IOP between 21 and 36 mmHg were randomized 3:1 intraoperatively to iStent *inject* implantation (treatment group, $n = 387$) or no stent implantation (control group, $n = 118$). The primary efficacy measure was defined as ≥20% reduction in unmedicated diurnal IOP at month 24 and was seen in 75.8% of treatment eyes versus 61.9% of control eyes ($p = 0.005$). The mean reduction in unmedicated diurnal IOP from baselines was greater in treatment eyes than in control eyes (7.0 ± 4.0 mmHg vs. 5.4 ± 3.7 mmHg, $p < 0.001$). Month 24 medication-free diurnal IOP ≤ 18 mmHg was achieved by 63.2% of treatment eyes compared with 50.0% of control eyes (difference 13.2%, 95% confidence interval 2.9–23.4). The safety profile of the treatment group was favorable and similar to that in the control group throughout the 2-year follow-up.

At this time, there have been no studies directly comparing the first- and second-generation iStent models. Glaukos has also launched the iStent *inject W* in Europe in 2020, which is a slight modification of the iStent *inject* with a wide flange at its base, allowing for enhanced visualization during implantation. In addition, the wider flange of the iStent *inject W* improves the predictability of the surgery, by minimizing the risk of "over-implanting" the device which results in the inlet being occluded by trabecular tissue.

3.5 Off-Label Use

Currently, the iStent is approved for use in combination with cataract extraction in the United States, but is licensed for standalone use in Europe. As described previously, Bahler et al. found that the implantation of more than one stent into the canal of cultured human anterior segments provided additional pressure lowering to that achieved with a single stent, but to a lesser degree [10]. Several studies and case reports have since been published demonstrating the efficacy of implanting multiple stents [28–32]. Most notably, Katz et al. conducted a prospective, randomized study of one, two, or three trabecular bypass stents in patients with open-angle glaucoma on topical hypotensive medication [33]. Stent placement was performed as a stand-alone procedure in either phakic or pseudophakic eyes. The initial results were

Table 3.3 Summary of additional trabecular micro-bypass clinical studies

Study	Design	Procedure	n	Follow-up (months)	IOP reduction mmHg (treatment)	IOP reduction mmHg (control)	Medication reduction (treatment)	Medication reduction (control)
Multiple stents								
Fernandez-Barrrientos et al. [46]	RCT	Phaco + 2 stents	17	12	7 (27%)	4 (16%)	1.1 (100%)	0.5 (42%)
Belovay et al. [21]	NRS	Phaco + 2–3 stents	53	12	4 (20%)	–	2.0 (74%)	–
iStent alone								
Spiegel et al. [47]	CS	1 stent	6	12	5 (25%)	–	19%	–
Buchacra et al. [48]	NRS	1 stent	10	12	7 (27%)	–	1.1 (62%)	–
Ahmed et al. [31]	NRS	2 stents + travoprost	39	18	10 (47%)	–	1.0 (50%)	–
Katz et al. [33]	RCT	1–3 stents	119	18	1: 10.1 (40.4%) 2: 11.4 (45.6%) 3: 12.4 (49.4%)	–	Decrease of mean IOP shown for patients without medication	–
Donnenfeld et al. [49]	NRS	2 stents	76	36	8.9 (36.9%)	–	89.7% not requiring medication	–
iStent inject								
Fea et al. [25]	RCT	2 stents	94	12	8 (38%)	8 (36%)	N/A[a]	N/A[a]
Arriola-Villalobos et al. [50]	CS	Phaco + 1–2 stents	20	12	9 (36%)	–	1.0 (77%)	–
Voskanyan et al. [26]	NRS	2 stents	99	12	10 (40%)	–	71.7% not requiring medication	–
Klamann et al. [28]	CS	2 stents	35	6	POAG: 7.0 (33.0%) PXG: 8.42 (35.5%)	–	POAG: 1.31 (60%) PXG: 1.29 (55%)	
Arriola-Villalobos et al. [51]	CS	Phaco + 2 stents	20	47 (mean)	9.74 (36.9%)	–	0.55 (42%)	–

Note: The value under medication reduction refers to the decrease in the mean number of hypotensive agents, followed by the mean percent reduction from baseline

Abbreviations: *RCT* randomized clinical trial, *CS* case series, *NRS* non-randomized study, *IOP* intraocular pressure, *phaco* phacoemulsification, *POAG* primary open-angle glaucoma, *PXG* pseudoexfoliative glaucoma

[a]Medical therapy control group

reported in 2015 with a total of 38 subjects receiving 1 stent, 41 subjects with 2 stents, and 40 with 3 stents. They were randomly assigned with a postmedication-washout baseline IOP ranging between 22 and 38. At 18 months, unmedicated mean IOP was 15.9 ± 0.9 with 1 stent, 14.1 ± 1.0 with 2 stents, and 12.2 ± 1.1 with 3 stents. Both the IOP reduction and decrease in medication use were found to be significantly greater with each additional stent. In 2018, the 42-month outcomes were reported [34]. By comparison, month 12 saw IOP reduction ≥ 20% without medication achieved in 89, 90, and 92% or one-, two-, and three-stent eyes, respectively; whereas month 42 showed the same reduction in 61, 91, and 91% of eyes. Based on the data available thus far, the additional reduction in both IOP and topical ocular hypotensive use seen with multiple stent implantation shows promise for iStent use in patients with more advanced disease and further prospective study is warranted. In addition, potential long-term health resource use may be reduced with the improved IOP control achieved with multiple stent placement versus more traditional treatment modalities such as selective laser trabeculoplasty or topical medications [35].

iStent implantation in phakic patients and after previous filtering surgery has also been evaluated [30, 31]. A prospective study by Ahmed et al. involved 39 phakic patients with unmedicated baseline IOP between 22 and 38 mmHg. Patients received two stents placed through a clear corneal incision. The mean unmedicated IOP decreased from 25.3 ± 1.8 mmHg preoperatively to 17.1 ± 2.2 mmHg at 13 months postoperatively [31]. Ferguson et al. inserted a single iStent in a retrospective series of 42 pseudophakic eyes. Medication use was reduced or unchanged in 80% of patients at 1 year, although not of statistical significance. In addition, mean IOP at 2 years was noted to improve from 20.26 ± 6.00 mmHg to 13.62 ± 4.55 ($p < 0.01$) [36].

Angle closure is currently a contraindication for iStent implantation. At present, only one prospective study has evaluated the safety and efficacy of iStent implantation in angle-closure eyes. Hernstadt et al. showed that the mean postoperative IOP decreased from 17.5 ± 3.8 mmHg to 14.8 ± 3.9 mmHg in 37 eyes with angle-closure disease 1 year after combined iStent trabecular micro-bypass device and phacoemulsification ($p < 0.001$). There were no sight-threatening intraoperative or postoperative complications reported, but iStent occlusion with iris occurred in 27% of eyes [37]. However, it was not possible to determine the additional effect of iStent implantation in lowering the IOP compared with phacoemulsification alone. A randomized study comparing phacoemulsification alone with the combined procedure in angle-closure eyes showed that the combined procedure was associated with a higher likelihood of complete success (87.5% [95% CI 58.6-96.7%] vs 43.8% [95% CI 19.8-65.6%]) [52].

A summary of additional trabecular micro-bypass clinical studies to date is demonstrated in Table 3.3 and illustrates the efficacy of iStent alone, multiple stents, as well as the previously discussed iStent *inject*.

3.6 Conclusion

Treating glaucoma patients has traditionally consisted of medications, laser, or filtering surgery. The well-known complications that may accompany trabeculectomy or tube shunt placement have led to the development of new therapeutic

approaches including the iStent and iStent *inject* implants. Although the reduction in intraocular pressure seen with these devices is not comparable to filtering surgery, a majority of patients can expect additional improvement versus cataract surgery alone. Another added benefit is seen in the potential reduction of ocular hypotensive medication dependency. As new long-term data become available, indications may expand to certain types of secondary glaucoma, use without concomitant phacoemulsification, and more advanced disease. Among minimally invasive glaucoma surgeries, the iStent currently provides a promising benefit for mild–moderate open-angle glaucoma patients with a favorable safety profile and sparing of conjunctival tissue should more aggressive intervention be necessary in the future.

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