Randomized Evaluation of the Trabecular Micro-Bypass Stent with Phacoemulsification in Patients with Glaucoma and Cataract

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Objective: To assess the safety and efficacy of the iStent trabecular micro-bypass stent (Glaukos Corporation, Laguna Hills, CA) in combination with cataract surgery in subjects with mild to moderate open-angle glaucoma.

Design: Prospective, randomized, open-label, controlled, multicenter clinical trial.

Participants: A total of 240 eyes with mild to moderate open-angle glaucoma with intraocular pressure (IOP) ≤24 mmHg controlled on 1 to 3 medications were randomized to undergo cataract surgery with iStent implantation (treatment group) or cataract surgery only (control). Fifty additional subjects were enrolled to undergo cataract surgery with iStent implantation under protocol expansion. Data in this report are based on the first 240 eyes enrolled.

Intervention: Implantation of the iStent trabecular micro-bypass stent in conjunction with cataract surgery or cataract surgery only.

Main Outcome Measures: The primary efficacy measure was unmedicated IOP ≤21 mmHg at 1 year. A secondary measure was unmedicated IOP reduction ≥20% at 1 year. Safety measures included best-corrected visual acuity (BCVA), slit-lamp observations, complications, and adverse events.

Results: The study met the primary outcome, with 72% of treatment eyes versus 50% of control eyes achieving the criterion ($P<0.001$). At 1 year, IOP in both treatment groups was statistically significantly lower from baseline values. Sixty-six percent of treatment eyes versus 48% of control eyes achieved ≥20% IOP reduction without medication ($P = 0.003$). The overall incidence of adverse events was similar between groups with no unanticipated adverse device effects.

Conclusions: Pressure reduction on fewer medications was clinically and statistically significantly better 1 year after stent plus cataract surgery versus cataract surgery alone, with an overall safety profile similar to that of cataract surgery alone.

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**Group members listed online in Appendix 1 (available at http://aaojournal.org).*

Glaucoma is a highly prevalent disease, diagnosed in more than 2 million people in the United States,[1] estimated to affect more than 60 million people worldwide by 2010,[2] and the second leading cause (after cataract) of vision loss in adults.[3] Glaucoma is a progressive disease that may lead to irreversible ganglion cell damage resulting in vision loss and impairment. The objective of glaucoma management is to preserve visual function by providing a significant and sustained decrease in intraocular pressure (IOP), using treatments that ensure patient compliance and possess favorable safety profiles. There are currently no ideal methods of treatment that meet each of these criteria. Consequently, significant research efforts are under way to develop treatment methods that improve on what is currently available.

Currently available treatments to lower IOP, such as ocular hypotensive medication,[4] laser trabeculoplasty,[5] and incisional glaucoma surgery,[6] have been shown to attenuate disease progression but are associated with complications that limit therapeutic potential. Pharmacotherapy is challenging because it requires compliance with prescribed dosing regimens,[7,8] proper instillation,[9,10] persistence,[11] and, in a typically elderly population, proper use concomitantly with multiple systemic medications.[12] Medications may cause local tolerability issues, and chronic application of preserved medications may result in ocular surface disease.[13] Laser trabeculoplasty, although generally safe, is occasionally associated with pain and inflammation, and has a limited magnitude and durability in some patients.[14] Incisional glaucoma surgeries that remove tissue or use an

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ab-externo device to filter fluid to reduce IOP are associated with numerous complications, including infection, inflammation, vision loss, bleb leak, bleb encapsulation, hypotony, cataract, and the need for subsequent surgery,[6,15–17] and may require the use of extemporaneously prepared off-label antifibrotic agents.[18] Filtration surgery may require frequent postoperative visits for care, including scleral flap suture lysis and anterior chamber reformation. Perhaps most concerning is the fact that such procedures may have devastating vision-threatening complications, such as bleb-related endophthalmitis many years after seemingly successful surgery. Because of their invasiveness and association with complications more serious than those associated with medication, such surgical techniques are not preferred treatment methods for earlier stages of the disease.

Cataract surgery alone has been shown to result in a modest reduction in IOP.[19–24] This IOP reduction may be explained by reversal of the compression of the ciliary body and narrowing of the trabecular plates and walls of Schlemm's canal, caused by the enlarged cataractous lens, when removed and replaced with a thinner IOL.[24] This reduction in IOP after cataract surgery has been shown to occur in normal, ocular hypertensive, and glaucomatous eyes. As a result, cataract surgery alone has been suggested as a treatment for managing IOP in patients with glaucoma with early or moderate disease.[19–21,23,24]

Research in the physiology of the trabecular meshwork in normal and diseased eyes suggests that the trabecular meshwork is the primary site of aqueous outflow and increased outflow resistance, and thus reduced outflow facility in primary open-angle glaucoma.[25–27] In an effort to bypass the diseased meshwork while maintaining the natural outflow pathway, Spiegel and Kobuch[28] implanted a simple silicone tube in 5 patients with uncontrolled open-angle glaucoma to achieve IOP and medication reduction. More recently, a titanium, L-shaped trabecular micro-bypass stent (iStent, Glaukos Corporation, Laguna Hills, CA) was designed to create a patent bypass through the trabecular meshwork to facilitate physiologic outflow and thus lower IOP (Fig 1).[29] In human anterior segments in vitro, implantation of the iStent reduced IOP and increased outflow facility.[30] The iStent has been evaluated in several pilot studies in patients with open-angle glaucoma.[31–33] A small comparative study of the iStent found implantation at the time of cataract surgery in patients with coexistent glaucoma to be significantly more effective than cataract surgery alone in reducing IOP and medication use.[34]

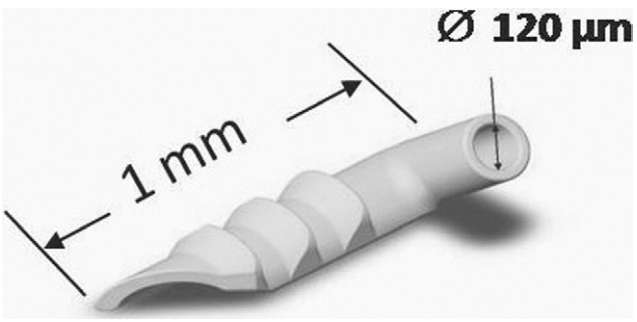

Figure 1. Glaukos iStent trabecular micro-bypass stent (Glaukos Corporation, Laguna Hills, CA).

For this new device, we conducted a large comparative study in patients with open-angle glaucoma already undergoing planned surgery for removal of existing cataracts by phacoemulsification to measure the incremental effect from iStent implantation over that of cataract surgery alone and to determine the potential benefit of combining 2 therapeutic treatments into 1 surgical event.

Materials and Methods

Study Design

This was a prospective, randomized, open-label, multicenter, controlled US Investigational Device Exemption clinical trial conducted at 29 US investigational sites (see Appendix 1, available at http://aaojournal.org). Patients were randomized into 1 of 2 treatment groups: stent implantation in conjunction with cataract surgery (treatment group) or cataract surgery alone (control group). We report the first year of follow-up on all randomized patients. The study protocol was approved by the institutional review board at each investigational site, and all study subjects provided written, informed consent. The protocol was amended in July 2007 after 240 eyes were enrolled, to enroll, after completion of the randomized phase, an additional 50 patients receiving the stent to collect additional safety data. This report is limited to a summary of data from the initial 240 eyes.

Subject Population

At each of the investigational sites, subjects were selected from the adult population of patients who presented with the need for cataract surgery, defined as clinically significant cataract with a best-corrected visual acuity (BCVA) of 20/40 or worse in the presence of glare. To be included in the study, subjects were required to have mild or moderate open-angle glaucoma confirmed by gonioscopy, with definitive characteristic visual field or nerve pathology, a cup/disk ratio of 0.8 or less, and IOP $\leq$24 mmHg while taking 1 to 3 ocular hypotensive medications, with a stable medication regimen for $\geq$2 months. After a washout of ocular hypotensive medication, IOP was required to be $\geq$22 mmHg and $\leq$36 mmHg during normal office hours. Medication washout periods were 5 days for carbonic anhydrase inhibitors, 2 weeks for α-adrenoceptor agonists, and 4 weeks for β-adrenoceptor antagonists and prostaglandin analogues. Excluded were individuals with severe glaucomatous field defects; severely uncontrolled IOP; angle-closure glaucoma; neovascular, uveitic, or angle recession glaucoma; prior glaucoma surgery other than iridectomy; prior refractive procedures; known corticosteroid responders; ocular disease that would affect safety; monocular subjects; or those with fellow eye BCVA worse than 20/200. Patients who met the inclusion and exclusion criteria were consecutively enrolled in the study. If both eyes qualified, then the study eye was selected at the investigator's discretion. Each patient was to participate with only 1 eye. Fellow eyes were to be treated for cataract and glaucoma consistent with each investigator's standard medical practice.

Trabecular Micro-Bypass Stent

The iStent is manufactured from titanium (Ti6A14V ELI) in a single-piece design and is heparin coated (Duraflo, Edwards LifeSciences, Irvine, CA). At 1.0 mm in length and 0.33 mm in height, with a snorkel length of 0.25 mm and a nominal snorkel

bore diameter of 120 μm, the iStent is the smallest medical device known to be implanted into the human body. It is manufactured in both a right- and left-eye model to facilitate ease of implantation. During the manufacturing process, the stent is attached to the end of a disposable insertion instrument. The inserter is designed to hold the implant and to release the implant once inserted nasally within Schlemm's canal. The stent and inserter are sterilized by gamma radiation.

Surgical Technique

All investigators underwent a wet lab training program on the surgical technique before performing stent implantation surgery. Each surgeon used standard phacoemulsification techniques through a clear corneal incision or limbal incision. Preoperative medications were to include a fluoroquinolone antibiotic (4 times 1 day preoperatively, then 30 minutes before surgery). Anesthesia was topical (49%), peribulbar (27%), retrobulbar (24%), or general (1 subject). For those patients randomized to the treatment arm, the stent was implanted after uncomplicated phacoemulsification and IOL implantation. If after cataract surgery, the surgeon thought that the pupil remained excessively dilated, an intracameral miotic was allowed. The patient's head and the microscope were then repositioned, and the angle was inspected with a gonioprism to ensure a good view of the trabecular meshwork in the nasal region. Additional viscoelastic was injected into the anterior chamber as needed to assist with chamber maintenance. The stent was inserted through the same temporal incision used for cataract surgery. The anterior chamber was traversed with the inserter (implant on tip of inserter) to approximately the pupillary margin and then positioned with the assistance of a gonioprism. The leading edge of the device was inserted through the trabecular meshwork and into the nasal aspect of Schlemm's canal with the tip of the implant directed inferiorly. The device was released by pushing the button on the inserter. After the device was fully released and within the Schlemm's canal, the inserter was withdrawn. Viscoelastic was removed and the anterior chamber was inflated with saline solution as needed to achieve physiologic pressure. Topical ocular hypotensive medication (apraclonidine) was to be administered at the end of the procedure. Eyes in which complications occurred during the cataract surgical procedure (e.g., posterior capsule rupture) were exited from the study at the conclusion of cataract surgery, regardless of the treatment group to which they were randomly assigned. Postoperative care included a topical fluoroquinolone antibiotic for 1 week and a tapering dose (starting with 6 drops per day) of prednisolone acetate 1% for 4 weeks.

Examinations

At the screening visit (pre-washout), following the informed consent process, the examination included slit-lamp biomicroscopy, indirect ophthalmoscopy, manifest refraction, measurement of IOP (using a 2-person method: 1 to perform the measurement and 1 to record the value),[35] and BCVA (via Snellen chart using a Brightness Acuity Tester at the medium glare setting). After washout of ocular medications, a baseline examination was performed that also included measurement of IOP, BCVA (logarithm of the minimum angle of resolution [logMAR], via Early Treatment of Diabetic Retinopathy Study system), and a repeated manifest refraction. If an individual met the IOP requirements, he/she was assigned treatment according to a computer-generated randomization schedule (PROC PLAN, PC-SAS, SAS Inc., Cary NC) and scheduled for surgery. Patients were examined at 3 to 7 hours; 1 day; 1 to 2 weeks; and 3, 6, 12, 18, and 24 months after surgery. For follow-up, BCVA was measured using the Early Treatment of Diabetic Retinopathy Study system. Examinations in the early postoperative period (within 1 month of surgery) consisted mainly of safety assessment. Automated static threshold visual fields (Humphrey 30-2 or 24-2, SITA standard) were assessed at baseline and 6, 12, and 24 months postoperatively. Per the study protocol, ocular hypotensive medication was to be added when IOP exceeded 21 mmHg or for visual field or optic nerve findings. Medications could also be removed and restarted using these criteria.

Outcome Measures

Outcome measures were established before commencing the study. The primary efficacy outcome measure was the proportion of patients with IOP $\leq$21 mmHg without ocular hypotensive medication 1 year postoperatively. The proportion of patients with a $\geq$20% reduction in IOP from baseline without medication was selected as the secondary efficacy outcome. Additional efficacy measures included categorical and continuous analysis of IOP and ocular hypotensive medication use, and Kaplan–Meier survival analysis of time to first use of ocular hypotensive medication.

Safety analyses included assessment of loss of BCVA of 1 line or greater (i.e., 5 letters logMAR) 3 months or more postoperatively, secondary surgical intervention, infection, elevated IOP requiring treatment with oral or intravenous medication or surgical intervention, stent obstruction, and other complications. Additional safety parameters included slit-lamp biomicroscopic observations and BCVA 1 year postoperatively.

Sample Size Calculations

A priori, a sample size of 90 per group was estimated to provide 80% power and a 1-sided significance level of 0.05 to detect a 19.5% difference in the primary efficacy outcome between groups (i.e., 55% responder rate in the treatment group vs. 35.5% in the control group). To ensure availability of follow-up data at 1 year on at least 90 subjects in each group, enrollment of 110 patients per group was planned.

Statistical Analyses

The primary efficacy population was an intent-to-treat (ITT) population consisting of all randomized eyes, analyzed according to the group to which they were randomized and irrespective of adverse events, using a last-observation-carried-forward analysis. In patients exited from the study before the 12-month visit or in patients missing the 12-month visit, the last available IOP value was used. Cases of secondary surgical interventions that potentially could affect the IOP (e.g., stent repositioning or explantation, trabeculoplasty or other glaucoma procedures, IOL replacement) were treated as nonresponders. Additional analysis populations included an as-treated population ([ATP], excluding those patients with major protocol deviations or missing data at 1 year; Fig 2, available at http://aaojournal.org) and a safety population of all eyes that underwent cataract surgery. A 1-sided z-test was used to compare the primary and secondary efficacy outcomes between the 2 study groups. Fisher exact tests were used to compare categoric outcomes between study groups. Two-sample *t* tests were used to compare continuous outcomes between study groups. All statistical tests were performed by PC-SAS (Version 9.1.3). The limit of statistical significance was set at $P \leq 0.05$, and no adjustments were made for multiple comparisons.

Results

Enrollment and Disposition

Enrolled in the randomized phase of the study between April 2005 and June 2007 were 240 eyes, which constituted the ITT population. No site enrolled more than 15% of subjects, and 10 sites enrolled 10 or more subjects. Of the 117 randomized to iStent implantation in conjunction with cataract surgery, 111 of these underwent cataract surgery with stent implantation. In the remaining 6 subjects randomized to the treatment group, a stent was not implanted because of complications of cataract surgery (n = 4), inability to implant a stent (n = 1), or termination from the study before undergoing treatment (n = 1). Of the 111 subjects implanted with an iStent, 106 completed the 12-month postoperative visit. Of the 5 subjects not examined at 12 months, 1 subject missed the visit, and 4 subjects were terminated from the study after withdrawal of consent because of poor health (n = 1), investigator withdrawal of subject because of poor health (n = 1), or death (n = 2), which in each case was deemed by the investigator to be unrelated to the treatment. Of the 123 subjects randomized to receive cataract surgery only, 117 subjects underwent cataract surgery. Six subjects did not undergo surgery because of withdrawal from consent before surgery (n = 4), baseline examination failure (n = 1), or termination from the study before treatment (n = 1). Three subjects exited the study after cataract surgery because of complications of cataract surgery. Of the remaining 114 subjects, all but 2 returned for the 12-month visit; 1 subject terminated from the study because of poor health, and 1 subject died. At the 12-month visit, subject accountability was 97% (106/109) in the treatment group and 99% (112/113) in the control group (Fig 2; available at http://aaojournal.org). The ATP consisted of 196 eyes (95 treatment and 101 control), and the safety population consisted of 233 eyes (111 treatment and 122 control).

Pre-Study Characteristics

Overall, demographics and preoperative characteristics were well matched for the treatment and control groups, with no differences between groups. Of the subjects, the mean age was 73 years, with 67% aged ≥70 years. Most subjects were female (59%; n = 142). The majority were white (71%; n = 171) with the remainder comprising black or African American (14%; n = 34), Hispanic or Latino (13%; n = 31), American Indian or Alaska Native (1%; n = 2), Asian (<1%; n = 1), and Native Hawaiian or Pacific Islander (<1%; n = 1) (Table 1, available at http://aaojournal.org). In addition to cataracts and glaucoma, frequent preexisting comorbid ocular conditions included posterior vitreous detachment (18%, 42), dry eye (13%, 31), and age-related macular degeneration (10%, 25); these were distributed similarly between groups. This patient population had moderate glaucomatous disease as evidenced by visual fields measured via mean deviation (−3.74±3.47 dB). Pseudoexfoliative glaucoma was reported in 6% of patients (n = 14), and pigmentary glaucoma was reported in 3% of patients (n = 7). At the screening visit, mean medicated IOP was 18.4±3.2 mmHg. The number and classification of preoperative topical ocular hypotensive medications were similar between groups (Table 2, available at http://aaojournal.org). Before washout, the mean number of medications was 1.5±0.6, with 75% of patients (n = 179) in both groups using a prostaglandin analog, 37% (n = 89) using a β-adrenoceptor antagonist, 24% (n = 58) using a carbonic anhydrase inhibitor, 14% (n = 34) using an α-adrenoceptor agonist, and < 1% (n = 2) using a miotic. Most patients (60%; n = 144) were using 1 ocular hypotensive medication. After washout, mean IOP was 25.4±3.6 mmHg and mean visual acuity (logMAR) was 0.36±0.23.

Stent Implantation

Use of an intraoperative intracameral miotic agent was reported in a higher proportion of subjects in the treatment group (64%,74/117) compared with the control group (24%, 28/123), consistent with the protocol recommendation for iStent implantation. Implantation of the iStent was successful in all but 1 patient in whom there was poor angle visualization. Other intraoperative complications specifically related to implantation of the stent included 8 cases (7%) of iris touch, 1 case of endothelial touch, 1 case of inadvertent implantation into the anterior chamber (the stent was retrieved and another stent was successfully implanted during the same surgery), and 1 case of stent malposition (a second stent was implanted during the same surgery) with no apparent impact on outcomes.

Efficacy

The proportion of subjects achieving the primary efficacy outcome of an IOP ≤21 mmHg without ocular hypotensive medications at 12 months (ITT, last-observation-carried-forward) was clinically and statistically significantly greater in the treatment group, 72% (84/117, 90% confidence interval [CI], 65–79), than in the control group, 50% (62/123, 90% CI, 43–58, $P < 0.001$, Fig 3). The proportion of patients achieving the secondary efficacy end point of IOP reduction ≥ 20% without ocular hypotensive medications at 12 months was also clinically and statistically significantly greater in the treatment group, 66% (77/117, 90% CI, 59–73) than in the control group, 48% (59/123, 90% CI, 41–55, $P = 0.003$, Fig 4).

The efficacy of the treatment group on both the primary and secondary end points was consistently greater than the control group alone at all time points, with the treatment difference at 3 months continuing throughout the balance of the 12-month follow-up period. In addition, the proportion of subjects in the treatment group achieving IOP ≤18 mmHg without ocular hypotensive medications exceeded the proportion of subjects in the control group achieving IOP ≤21 mmHg without ocular hypotensive medications at every time point from 3 to 12 months. Furthermore, evaluation of available data at 12 months showed that the proportion of eyes meeting both the

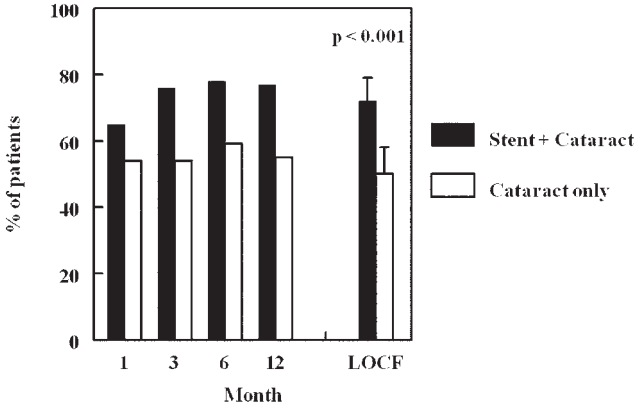

Figure 3. Proportion of patients with IOP ≤21 mmHg without ocular hypotensive medications (ITT). N = 108, 103, 101, 103, and 117, and 114, 112, 109, 110, and 123 for the stent + cataract and cataract surgery only groups at 1, 3, 6, and 12 months and last-observation-carried forward analyses, respectively. IOP = intraocular pressure; LOCF = last observation carried forward. ITT = intent-to-treat.

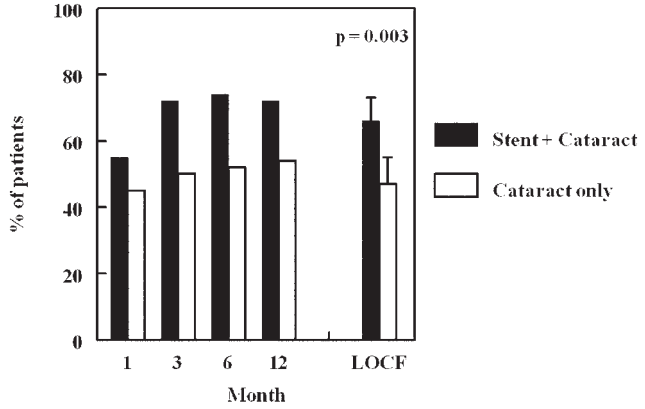

Figure 4. Proportion of patients with IOP reduction ≥20% without ocular hypotensive medications (ITT). N = 108, 103, 101, 103, and 117, and 114, 112, 109, 110 and 123 for the stent + cataract and cataract surgery only groups at 1, 3, 6, and 12 months and last-observation-carried forward analyses, respectively. IOP = intraocular pressure; ITT = intent-to-treat; LOCF = last observation carried forward.

primary and secondary outcomes (i.e., IOP ≤ 21 mmHg and IOP reduction ≥20% without anti-glaucoma medications) was higher in the treatment group than in the control group at every visit. At 12 months, 70% of treatment subjects (72/103) versus 50% of control subjects (55/110) had this outcome.

Analyses of medication use over time show that ocular hypotensive medications were initiated later in the postoperative period and used in a lower proportion of patients in the treatment group at every postoperative interval compared with patients in the control group. The Kaplan–Meier analysis shows the significant delay in medication introduction in the treatment group versus the control group ($P < 0.001$; log-rank; Fig 5, available at http://aaojournal.org). Less than 25% of patients in the treatment group were receiving medications at all visits, and only 15% were receiving medications at month 12. In contrast, the percent of patients in the control group receiving medications increased from 12% at 1 day to 37% at 7 days postoperatively. At month 12, 35% of control patients were taking medications ($P = 0.001$, Fig 6, available at http://aaojournal.org). Although medication use was lower in the treatment group, the type of medications used was proportionally similar in both groups. At month 12, 10% of patients in the treatment group versus 21% of patients in the control group used a prostaglandin analog; 6% versus 12% used a β-adrenoceptor antagonist, 4% versus 7% used a carbonic anhydrase inhibitor, and 2% versus 4% used an α-adrenoceptor agonist, respectively (Table 2, available at http://aaojournal.org). These data show a consistent approach in the type of medication added back postoperatively in the treatment and control groups.

Although mean reduction in IOP appeared similar in both groups, a substantially higher level of medication was used in the control group to maintain this similar IOP level. The mean reduction in IOP at 12 months compared with the preoperative unmedicated baseline IOP was 8.4±3.6 mmHg in the treatment group versus 8.5±4.3 mmHg in the control group, representing a >30% reduction in IOP in both groups. Mean reduction in IOP at 12 months versus preoperative, medicated screening IOP was 1.5±3.0 mmHg in the treatment group versus 1.0±3.3 mmHg in the control group. The mean number of ocular hypotensive medications at 12 months was lower than in the control group (0.2±0.6 vs. 0.4±0.7; $P = 0.016$). Furthermore, the mean decrease in medications from screening was greater in the treatment group versus the control group (1.4±0.8 vs. 1.0±0.8; $P = 0.005$).

Safety

Ophthalmic findings in the immediate postoperative period included transient events expected after cataract surgery, such as corneal edema, trace folds/striae, inflammation, epithelial defect, discomfort, and 1 case of transient hypotony at 5 to 7 hours that resolved without intervention by the 1-day postoperative period. The most frequent adverse events were similar in both groups (Table 3). Stent obstruction was reported in 4% of treatment subjects; all cases occurred within the first postoperative month and resolved within several weeks after subsequent surgery (n = 3) or without surgery (n = 1). Iritis was reported in 1% of patients in the treatment group versus 5% of patients in the control group. Only 1 adverse event in each group was deemed by investigators to be severe. One subject in the treatment group experienced BCVA loss to "count fingers" after retinal ischemia (and stroke) from carotid artery stenosis unrelated to ophthalmic surgery, and 1 patient in the control group experienced BCVA loss after vitrectomy for macular traction, macular hole, and macular edema. Paracentesis for elevated IOP was similar in both groups (Table 4), with the majority of eyes undergoing this procedure 1 day postoperatively for increased IOP ≥10 mmHg from baseline. Stent-related secondary surgical interventions were reported in 5 subjects (3 with stent repositioning, 1 with stent removal and replacement, 1 with laser iridoplasty) to resolve stent obstruction or malposition observed by investigators in the early postoperative period. In the control group, 2 subjects underwent laser trabeculoplasty; 1 subject underwent deep sclerectomy followed by revision and laser sclerostomy 5 weeks later; 1 subject underwent

Table 3. Frequently Reported Postoperative Ocular Complications (≥2%) through Month 12

Complication	iStent with Cataract Surgery N = 111	Cataract Surgery Only N = 122
Anticipated early postoperative event	14 (13%)	15 (12%)
Stent obstruction by iris, vitreous, fibrous overgrowth, fibrin, blood, and so forth	4 (4%)	0 (0%)
Posterior capsular opacification	3 (3%)	8 (7%)
Stent malposition	3 (3%)	0 (0%)
Subconjunctival hemorrhage	2 (2%)	2 (2%)
Elevated IOP, other	2 (2%)	1 (1%)
Epiretinal membrane	2 (2%)	1 (1%)
Iris atrophy	2 (2%)	0 (0%)
Blurry vision or visual disturbance	1 (1%)	6 (5%)
Iritis	1 (1%)	6 (5%)
Dry eye	1 (1%)	2 (2%)
Elevated IOP requiring treatment with oral or intravenous medications or with surgical intervention	1 (1%)	2 (2%)
Macular edema	1 (1%)	2 (2%)
Foreign body sensation	0 (0%)	3 (2%)
Allergic conjunctivitis	0 (0%)	2 (2%)
Mild pain	0 (0%)	2 (2%)
Rebound inflammation from tapering steroids	0 (0%)	2 (2%)

IOP = intraocular pressure.
"Anticipated, early postoperative events" included transient events such as corneal edema, trace folds, trace striae, transient hypotony at 5–7 hrs, inflammation, epithelial defect, and discomfort as expected after cataract surgery.

Table 4. Secondary Surgical Interventions (n and %) through Month 12

Secondary Surgical Intervention	iStent with Cataract Surgery N = 111	Cataract Surgery Only N = 122
Paracentesis	31 (28%)	33 (27%)
Nd:YAG laser capsulotomy	4 (4%)	7 (6%)
Stent repositioning	3 (3%)	0 (0%)
Punctal cautery/punctual plugs	1 (1%)	2 (2%)
Focal argon laser photocoagulation	1 (1%)	0 (0%)
Nd:YAG laser for stent obstruction	1 (1%)	0 (0%)
Stent removal and replacement	1 (1%)	0 (0%)
Trabeculoplasty	0 (0%)	2 (2%)
Deep sclerectomy/sclerostomy	0 (0%)	1 (1%)
IOL removal and replacement	0 (0%)	1 (1%)
LASIK	0 (0%)	1 (1%)
Pupilloplasty	0 (0%)	1 (1%)
Vitrectomy	0 (0%)	1 (1%)
Wound resuture due to wound leak	0 (0%)	1 (1%)

IOL = intraocular lens; LASIK = laser-assisted in situ keratomileusis; Nd:YAG = neodymium-doped yttrium aluminum garnet.

vitrectomy for macular traction, macular hole, and macular edema; and 1 subject underwent 3 separate procedures of wound resuture for a wound leak, pupilloplasty, and IOL removal and replacement. The overall rate of adverse events was similar between groups, with no unanticipated adverse device effects reported.

The majority of patients in both groups improved from their preoperative BCVA and maintained this improvement over the 1-year postoperative period. Preoperatively, 45% of patients in the treatment group versus 44% of patients in the control group achieved BCVA of ≥20/40. At 1 year, 94% of patients in the treatment group versus 90% of patients in the control group achieved BCVA of ≥20/40, and most of the patients had BCVA of ≥20/32 (85%, 89/105, and 79% [89/112], respectively). The percent of patients with improved BCVA (including within 1 line of preoperative BCVA) was 97% in the treatment group versus 95% in the control group.

Discussion

The iStent has been shown to improve aqueous outflow by means of a patent channel created through the trabecular meshwork into Schlemm's canal via ab-interno placement of the device. The ocular hypotensive efficacy seen with the stent in this study is consistent with the trabecular bypass mechanism of action and results described in previous work.[31–34] Reduction in IOP and medications was shown in earlier trials involving iStent implantation only or iStent implantation in conjunction with cataract surgery.

The goals in implanting the iStent through the same incision used for cataract surgery in patients with mild to moderate open-angle glaucoma were to (1) provide the additional therapeutic benefit of greater IOP control compared with that seen after cataract surgery alone; (2) add no significant additional risk to routine cataract removal, which is highly safe and performed more frequently in the United States than any other surgery; (3) optimize efficiency and safety by combining 2 therapeutic modalities into a single operative event; and (4) improve aqueous outflow in eyes before significant disease progression or destruction of viable tissue. This study was designed to examine the incremental benefits and risks of iStent combined with cataract surgery compared with those of cataract surgery alone. To our knowledge, this is the first large-scale randomized, controlled, multicenter trial of cataract surgery with a glaucoma drainage device versus cataract surgery alone.

In this study of the iStent, when used in conjunction with cataract surgery in subjects with mild to moderate open-angle glaucoma, we found a statistically and clinically significant treatment effect in favor of the iStent in reducing IOP with less medication use compared with cataract surgery alone. At 12 months after implantation, there was a 22% treatment difference (72% vs. 50%, $P < 0.001$) in favor of the iStent in the proportion of patients with IOP ≤21 mmHg without ocular hypotensive medications at 12 months.

This primary end point selected for this clinical trial, IOP ≤21 mmHg with no medications, is recognized as clinically meaningful by the ophthalmic community.[36] Reducing IOP to ≤21 mmHg without medication has been used as a definition of surgical success in glaucoma practice and clinical trials,[37–43] and although target IOP varies for individual patients, it is common for physicians to manage patients with glaucoma with mild to moderate disease to target pressures. For these reasons, achieving a target IOP without medication is generally recognized as an important clinical benefit. Thus, use of the iStent in conjunction with phacoemulsification provided a clinically meaningful benefit of reducing IOP to ≤21 mmHg without medication to a greater extent than with phacoemulsification alone. In addition, the proportion of iStent subjects achieving IOP ≤18 mmHg with no medications exceeded that of cataract only subjects achieving IOP ≤21 mmHg without medication from 3 to 12 months postoperatively.

In this study, there was an 18% treatment difference (66% vs. 48%, $P = 0.003$) in the proportion of patients in the iStent group with a reduction of IOP by 20% without ocular hypotensive medications compared with the control group. A 20% IOP reduction is considered by the American Academy of Ophthalmology to be a Level A recommendation, meaning that it is defined as "most important" to the patient care process.[44] By using this end point as a second measure of benefit, findings from this trial showed that most subjects had greater benefit from implantation of the iStent in conjunction with cataract surgery than from cataract surgery alone.

The time to first medication use was statistically significantly longer in the iStent group, with subjects taking more medications in the control group at 1 week than subjects in the iStent group at 1 year. Although the distribution in type of medication use was consistent among groups, there were only approximately half as many patients in the iStent group using prostaglandins, β-blockers, carbonic anhydrase inhibitors, or α agonists as in the cataract only group. These analyses of postoperative medication use suggest the iStent

may allow some patients to eliminate or significantly delay the use of prescription medication after cataract surgery.

The results showed that mean change in IOP was similar between groups. This was expected, because the protocol called for subjects in both groups to be managed consistently to an IOP of 21 mmHg or lower through the use of glaucoma medications. The key difference is that iStent subjects achieved their IOP reductions with fewer medications than those in the cataract surgery only group. The difference in medication use at 12 months (15% vs. 35%) was clinically and statistically significant and potentially meaningful to patients. Further, there was a mean reduction of 1.4 medications in the iStent plus cataract surgery group versus 1.0 medication in the cataract surgery only group. The lower proportion of iStent subjects taking medications and the between-group difference of 0.4 medications suggests that numerous iStent subjects benefitted from taking fewer medications than patients with cataract surgery only.

From a safety perspective, implantation of the stent did not result in substantial additional risk or adverse events. The glaucoma subjects enrolled in this study originally presented for cataract surgery with the goal of improving their vision, and this was achieved in ≥95% of subjects in both groups. Ophthalmic findings in the immediate and longer-term postoperative period were typical of cataract surgery and similar in both treatment groups. We did report relatively minor stent-related adverse events, which were fewer and less serious than those reported with traditional incisional trabeculectomy, canaloplasty, or ab-externo drainage devices in prior studies.[6,15–17,37–43,45,46]

Further, unlike trabeculectomy, patients receiving the iStent are not at risk for late-onset complications, such as bleb leak, bleb-related infection, or hypotony. Adverse events deemed severe by investigators occurred in only 2 patients; these events were unrelated to the iStent. The ocular and non-ocular adverse events for the iStent treatment and cataract only groups were considered representative of complications and conditions occurring in this elderly population with ocular and non-ocular comorbidities in addition to their ocular conditions of glaucoma and cataract. Although there were stent-related secondary surgical interventions, they were relatively few and occurred and resolved early in the postoperative period, and were not associated with additional morbidity to patients. Because of the microscopic size of the iStent, the initial implantation and the repositioning of the device are less invasive than with larger tubes or shunts. Stent implantation through the same incision used for cataract surgery is a relatively atraumatic, ab-interno procedure that spares the conjunctival tissue and thereby preserves future treatment options for patients who may require additional IOP-lowering surgery. In addition, by implanting the iStent at the time of cataract surgery, patients may benefit by delaying or avoiding the morbidity associated with a separate additional surgical intervention. Notably, the superior efficacy demonstrated in the iStent plus cataract surgery group was achieved with no compromise in visual outcomes or safety of the cataract surgery procedure and with a safety profile comparable to cataract surgery alone. Trabeculectomy and phacoemulsification, the most commonly combined cataract and glaucoma operations, each lower IOP by opposing mechanisms, one enhancing trabecular outflow while the other bypasses physiologic outflow. That is, the therapeutic benefit of one procedure may negate the beneficial effect of the other. In contrast, it is reasonable to believe that the iStent and phacoemulsification lower IOP by a similar mechanism, because each enhances trabecular outflow.

Previous studies have found a clinically significant decrease in IOP after cataract surgery via phacoemulsification in normal and glaucomatous eyes after the first postoperative year. For example, Shingleton et al[20] found a mean decrease of 1.11 mm, Kim et al[22] found a mean decrease of 2.9 mmHg, and Hayashi et al[23] found a mean decrease of 4.3 mmHg. More recent studies have found a larger decrease after cataract surgery. Work by Poley et al[24] showed that, depending on the preoperative IOP, IOP reduction was as great as 6.5 mmHg. In the present study, we observed a reduction in IOP that was similar for both groups. However, the IOP reduction in the iStent group was achieved with the use of fewer ocular hypotensive medication compared with the control group.

Study Limitations

There are several limitations in this study. The study was, by design, open-label, given that there was no way to mask the treatment to the surgeon during the surgical intervention, or to the observer at the time of gonioscopy. However, although the procedure was not masked, there is no way to see or identify the iStent at the slit lamp without gonioscopy; thus, the examiner was unable to tell to which group the patient belonged at the time of tonometry. For logistic reasons, we chose not to collect data on the nature of glaucoma and its treatment in the fellow eye. Thus, we were unable to evaluate changes in the fellow eye and how that might affect the study eye. We are aware of other surgical methods to bypass damaged trabecular outflow to create normal outflow,[45,46] or through choroidal outflow.[47] Comparison of the safety and efficacy of the stent with these other methods was not possible in this Investigational Device Exemption trial, because there is no approved competitive device for the intended indication. The population in this study was limited to early to moderate glaucoma with cataract; thus, the conclusions from this study would not apply to patients with mild to moderate glaucoma who do not require cataract surgery or to patients with advanced or severely uncontrolled glaucoma. Because all patients were included in the analyses, these data also incorporate the learning curve of the investigators. Finally, there was no postoperative medication washout in this study. However, a small series by Fea[34] comparing iStent plus cataract surgery with cataract surgery alone showed significantly lower IOP and medication use in the iStent group 15 months after surgery, as well as significantly lower IOP after subsequent medication washout. After a 1-month medication washout (16 months postoperative), an IOP reduction of 1.3 mmHg versus baseline was measured in the iStent group compared with an IOP increase of 1.9 mmHg from baseline in the control group, representing a 3.2 mmHg difference in treatment effect.

In conclusion, the implantation of the stent in patients undergoing cataract surgery provided clinically and statistically significant improvements in the management of elevated IOP compared with cataract surgery alone, with a favorable safety profile and clinically significant reductions in IOP and medication. Thus, the benefit of the iStent was shown to exceed the risk in subjects with mild to moderate open-angle glaucoma when implanted during cataract surgery. We suggest that the stent addresses many of the limitations and adverse events of current medical and surgical therapies, and that this represents a positive benefit–risk intervention in this patient population undergoing cataract surgery. The iStent is believed to reestablish natural trabecular outflow, and it leaves the conjunctiva untouched, and avoids the lifelong risk of complications associated with filtering blebs. Thus, iStent implantation in patients with mild to moderate open-angle glaucoma undergoing cataract surgery represents a novel therapeutic approach that provides clinically significant reductions in IOP and medication use. Pressure reduction with fewer medications was clinically and statistically significantly better 1 year after stent plus cataract surgery versus cataract surgery alone with an overall safety profile similar to that of cataract surgery alone.

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