

# Fluorophotometric Study of the Effect of the Glaukos Trabecular Microbypass Stent on Aqueous Humor Dynamics

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**PURPOSE.** To evaluate the changes in aqueous humor dynamics and the efficacy and safety of the iStent (Glaukos Corp., Laguna Hills, CA), in combination with cataract surgery.

**METHODS.** This investigation was a prospective, randomized, clinical study in patients with open-angle glaucoma or ocular hypertension who were undergoing cataract surgery. Aqueous flow ( $F$ ) and trabecular outflow facility ( $C_T$ ) were measured by fluorophotometry before surgery and at months 1, 6, and 12 in both groups.

**RESULTS.** Thirty-three eyes of 33 patients were randomized to either two stents and cataract surgery ( $n = 17$ , group 1) or cataract surgery alone ( $n = 16$ , group 2). Before surgery,  $F$  and  $C_T$  were similar in groups 1 and 2 ( $1.78 \pm 0.44$  and  $1.74 \pm 0.82$   $\mu\text{L}/\text{min}$ ,  $P = 0.18$ ;  $0.12 \pm 0.03$  and  $0.13 \pm 0.06$   $\mu\text{L}/\text{min}/\text{mm Hg}$ ,  $P = 0.71$ , respectively). After surgery, there were no changes of note in  $F$ , however,  $C_T$  increased in both groups. At 1 year,  $C_T$  was  $0.45 \pm 0.27$   $\mu\text{L}/\text{min}/\text{mm Hg}$  in group 1 and  $0.19 \pm 0.05$   $\mu\text{L}/\text{min}/\text{mm Hg}$  in group 2 ( $P = 0.02$ ), which represented increases of 275% and 46%, respectively. Mean IOP reduction was also greater in group 1 than in group 2 ( $6.6 \pm 3.0$  mm Hg vs.  $3.9 \pm 2.7$  mm Hg;  $P = 0.002$ ). The mean number of medications was significantly lower in group 1 than in group 2 ( $0.0$  vs.  $0.7 \pm 1.0$ , respectively;  $P = 0.007$ ).

**CONCLUSIONS.** Compared with cataract surgery alone, implantation of the iStent concomitant with cataract extraction significantly increased trabecular outflow facility, reduced IOP, and reduced the number of medications at 1 year. Longer follow-up is needed to assess the long-term effect on outflow facility. (ClinicalTrials.gov number, NCT00326066.) (*Invest Ophthalmol Vis Sci.* 2010;51:3327-3332) DOI:10.1167/iovs.09-3972

The abnormal obstruction of the trabecular meshwork to aqueous flow is believed to be the primary reason for increased resistance in the conventional outflow pathway, resulting in elevation of intraocular pressure (IOP) in open-angle

glaucoma (OAG). The site of abnormal outflow resistance within the meshwork is the juxtacanalicular tissue adjacent to Schlemm's canal, a layer of the meshwork approximately 10  $\mu\text{m}$  thick.<sup>1,2</sup> An ideal procedure would restore physiologic outflow by bypassing this thin layer of tissue, to achieve a significant clinical decrease in IOP without requiring manipulation of the sclera and the creation of a filtration bleb.

Many glaucoma therapies for lowering IOP are focused on rerouting the aqueous humor around the conventional outflow pathway. These include topical medications that increase uveoscleral outflow, filtration surgery, and implantation of glaucoma drainage devices. In recent years, nonpenetrating surgeries and aqueous shunts have been developed as an alternative to traditional glaucoma surgeries. The Glaukos trabecular microbypass (iStent; Glaukos Corp., Laguna Hills, CA) is a small, tubular, L-shaped device, implanted abinternally, allowing communication between the anterior chamber and Schlemm's canal. The objective of the implant is to bypass the site of abnormal outflow resistance.

The principal objective of this study was to use fluorophotometry to evaluate the changes in aqueous outflow facility after the iStent was implanted. The secondary objectives were to evaluate the changes in IOP and the incidence of possible complications during and after surgery.

## MATERIALS AND METHODS

Between January and June 2006, 33 eyes of 33 patients with POAG or ocular hypertension (OHT), who were recruited from the San Carlos Clinical Hospital's Department of Glaucoma, were included in this prospective, randomized, clinical evaluation. The study's protocol was approved by the San Carlos Clinical Hospital's Ethics Committee on Clinical Research, and the methods described adhered to the tenets of the Declaration of Helsinki. Informed consent was obtained from all participants before they were included in the study.

Each subject underwent a comprehensive ophthalmic examination, including review of medical history, best corrected visual acuity, slit lamp biomicroscopy, Goldmann applanation tonometry, gonioscopy, dilated funduscopy examination, and standard automated perimetry (Octopus 301 G1, tendency oriented perimetry algorithm [TOP<sup>3-5</sup>]; Haag-Streit AG, Köniz, Switzerland).

Eligible eyes were required to have a medicated IOP  $>17$  and  $<31$  mm Hg and an IOP  $>21$  and  $<35$  mm Hg after appropriate washout of hypotensive medications. Additional requirements were a cataract eligible for cataract surgery and visual acuity worse than 20/40. Table 1 shows the complete list of the inclusion and exclusion criteria. The patients were classified in groups according to the visual field findings and the staging system proposed by Mills et al.<sup>6</sup> using the conversion method of Zeyen.<sup>7</sup> Eligible patients were randomly assigned to one of the two treatment groups, with a computer-generated sequence: group 1 received two iStents and underwent cataract surgery, and group 2 underwent cataract surgery alone.

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TABLE 1. Inclusion and Exclusion Criteria

Inclusion criteria
18 years of age or older
IOP >17 and <31 mm Hg with treatment and >21 and <36 mm Hg after the pharmacologic washout period.
Cataract that requires surgery.
Scleral spur clearly visible with gonioscopy.
Has not undergone glaucoma incisional surgery or a laser procedure.
Minimum VA of 20/200 or better.
Authorization and signature on the informed consent.
Exclusion criteria
Younger than 18 years.
Closed-angle glaucoma.
Secondary glaucoma, non-neovascular, uveitic, or angular recession glaucoma.
Previous glaucoma procedures (e.g., trabeculectomy, viscocanalostomy, ALT, SLT, drainage implant, collagen implant, cyclodestruction procedure)
Threat of visual field fixation.
Cornea with opacity that impedes gonioscopy vision from the nasal angle.
Elevated episcleral venous pressure due to a history of thyroid orbitopathy, carotid cavernous fistula, orbital tumor, or congestive orbital illness.
Retrobulbar tumor.
Thyroid ocular illness.
Sturge-Weber syndrome.
Chronic inflammatory disease.
Previous ocular trauma.
Peripheral anterior synechiae in the area where the implant is inserted.
Glaucoma due to vascular disorder.
Ocular surface disorders.
Glaucoma due to burns with chemical elements.
Previous refractive surgery that makes intraocular pressure measures difficult (PRK, RK, LASIK, LASEK).

ALT, laser trabeculectomy; SLT, selective laser trabeculectomy; PRK, photorefractive keratectomy; RK, radial keratectomy; LASIK, laser in situ keratomileusis; LASEK, laser subepithelial keratomileusis.

Baseline and follow-up visits included best corrected visual acuity, slit lamp biomicroscopy, IOP measurement (baseline, days 1, 2, and 7-14 and months 1, 3, 6, and 12 after surgery), gonioscopy and goniophotography (before surgery and months 1, 6, and 12 after surgery), dilated funduscopic examination, measurement of aqueous flow ( $F$ ) and trabecular outflow facility ( $C_T$ ) by fluorophotometry (Fluorotron Master; Coherent, Palo Alto, CA; before surgery and months 1, 6, and 12 after surgery), standard automated perimetry (Octopus 301 G1, TOP; Haag Streit), and anterior chamber study (anterior chamber volume [ACV], anterior chamber distance [ACD], and anterior chamber angle [ACA]; Pentacam; Oculus Optikgeräte GmbH, Wetzlar, Germany).

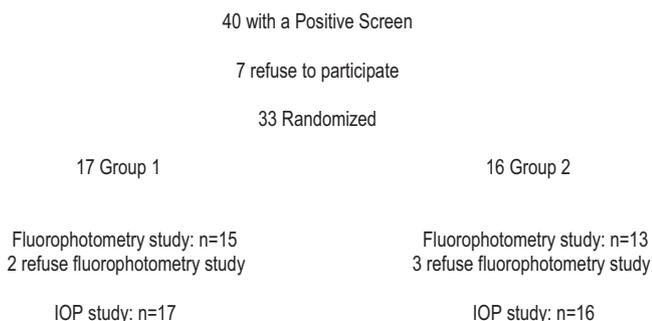


FIGURE 1. Flow diagram of the patients during the study.

TABLE 2. Baseline Characteristics of Study Population

Characteristic	Group 1	Group 2	P
Eyes, <i>n</i>	17	16	
Age			
Mean $\pm$ SD, y	75.2 $\pm$ 7.2	76.7 $\pm$ 5.8	0.5
Range, y	63-86	64-89	
Sex, female/male	11/6	7/9	0.3
Stage of glaucoma, <i>n</i> (%)			
0, Ocular hypertension	2 (11.8)	1 (6.3)	
1, Early glaucoma	7 (41.2)	11 (68.8)	0.5
2, Moderate glaucoma	4 (23.5)	3 (18.8)	
3, Advanced glaucoma	3 (17.6)	1 (6.3)	
4, Severe glaucoma	1 (5.9)	0 (0)	

All postoperative evaluations, except for the gonioscopies/goniophotographs (JMC), were performed by the same examiner (YFB), who was masked to the type of surgery performed.

All patients using ocular hypotensive medication during follow-up were subjected to a washout period before the fluorophotometry measurements, in accordance with the established treatment. At 11 AM, the patients received 0.25% fluorescein and 0.4% benoxinate HCl eyedrops (Fluotest; Alcon Laboratories, Fort Worth, TX), 1 drop every 2 minutes for 30 minutes. The subjects reported to the hospital at 3:30 PM the same day. Five measurements were made at 30-minute intervals from 3:30 PM to 5:30 PM.<sup>8,9</sup>  $F$  was calculated according to the method of Jones and Maurice,<sup>10</sup> as modified by Yablonski et al.<sup>11</sup>  $C_T$  was obtained from the equation

$$F_{in} = F_{out} = C_T(IOP - P_{ev}) + F_u \quad (1)$$

where  $F_{in}$  is the total inflow of aqueous humor;  $F_{out}$  is the outflow of aqueous humor;  $F_{in} = F_{out} = F = K_o \times V_a$  (where,  $K_o$  is a coefficient that refers to the outflow of fluorescein from the anterior chamber, and  $V_a$  is the anterior chamber volume);  $P_{ev}$  is episcleral pressure; and  $F_u$  is uveoscleral aqueous flow. If  $F_u$  is assumed to be negligible<sup>12</sup> ( $F_u = 0.3 \mu\text{L}/\text{min}$ ) then

$$C_T = F/(IOP - P_{ev}) \quad (2)$$

This assumption<sup>13</sup> may have introduced a certain systematic error into the calculation of  $C_T$  in both groups.  $P_{ev}$  was assumed to be 10 mm Hg.<sup>14</sup>

The iStent is manufactured of titanium and is heparin coated (Duraflon powder; Duraflon, Indianapolis, IN). It is L-shaped, measures  $1 \times 0.33$  mm with a nominal snorkel bore diameter of 120  $\mu\text{m}$  and is designed to fit within Schlemm's canal. The tip of the stent allows penetration through the meshwork during insertion. Three retention ridges along the half-pipe portion securely place the microbypass in Schlemm's canal. The weight of the stent is less than 0.1 mg. The stent is preloaded in a 26-gauge insertion device. The tip of the inserter advances through the trabecular meshwork and into Schlemm's canal, leaving the proximal end of the stent visible in the anterior chamber.

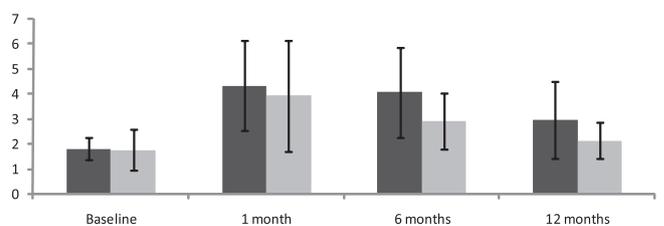
FIGURE 2. Mean aqueous flow rate ( $F$ ) determined by fluorophotometry over the time in groups 1 (black) and 2 (gray).

TABLE 3. Trabecular Outflow Facility

	Group 1		Group 2		<i>P</i>
	Mean ± SD	Change ± SD	Mean ± SD	Change ± SD	
Preoperative	0.12 ± 0.03	—	0.13 ± 0.06	—	0.71*
1 mo	0.88 ± 0.94	0.75 ± 0.94	0.41 ± 0.25	0.27 ± 0.27	0.18†
6 mo	0.88 ± 0.54	0.75 ± 0.54	0.38 ± 0.42	0.25 ± 0.42	0.04†
12 mo	0.45 ± 0.27	0.32 ± 0.16	0.19 ± 0.05	0.05 ± 0.08	0.02†

Data are the mean  $C_T$  ( $\mu\text{L}/\text{min}/\text{mm Hg}$ ) and change from baseline ± SD.

\* Group 1 versus group 2.

† Incremental time study between group 1 and group 2.

All surgeries were performed by two surgeons (JGF, JMC). In all cases, topical anesthesia was used (1 mg/mL tetracaine chloride and 4 mg/mL oxybuprocaine chloride; Colicursí Anestésico Doble; Alcon Cusí, Barcelona, Spain) as was intracameral anesthesia (0.2 mL of 1% lidocaine chloride). Cataract extraction via phacoemulsification was performed through a temporal 2.8-mm corneal incision with an acrylic intraocular lens implanted in the capsular bag (XL StabiSKY; Carl Zeiss Meditec, Oberkochen, Germany). After IOL implantation, additional steps to implant two stents in the group 1 eyes were as follows: Acetylcholine was injected into the anterior chamber (1% acetylcholine Cusí; Alcon Cusí). Cohesive viscoelastic (Healon, 10 mg of NaHA; AMO Inc., Madrid, Spain) was used to maintain the anterior chamber during implantation of the iStents. Trabecular angle visualization was facilitated by rotating the patient's head 45°, and a Swan-Jacobs gonioscope was used. The first stent was implanted in the lower nasal quadrant midway between the 5 and 6 o'clock positions in the right eye and midway between 6 and 7 o'clock in the left eye. The second stent was implanted in the upper nasal quadrant, midway between the 2 and 3 o'clock positions in right eyes and midway between 9 and 10 o'clock in left eyes. Once the stents were implanted, the viscoelastic was aspirated, and the corneal incision was hydrated.

All the patients were subjected to a washout period before surgery; the ocular hypotensive medication was reintroduced after surgery according to the criteria of the investigator. Patients on hypotensive medication in the fluorophotometry study were subjected to a washout period before the preoperative fluorophotometry and throughout follow-up.

### Statistical Analysis

Because of the small study sample, continuous variables, expressed as the mean ± SD, were analyzed with the Mann-Whitney nonparametric test. Categorical variables were compared by means of  $\chi^2$  analysis. Temporal changes in postoperative IOP, aqueous outflow facility, and aqueous humor flow rate were compared by repeated-measures analysis of variance (MANOVA) or the nonparametric Friedman test. The null hypothesis was rejected in each statistical test when  $P < 0.05$  (statistical analyses: SPSS software ver. 12.0 for Windows; SPSS Inc., Chicago, IL; and MedCalc, ver. 7.3; MedCalc, Mariakerke, Belgium).

The sample size was calculated to detect a 0.3- $\mu\text{L}/\text{min}/\text{mm Hg}$  difference in the outflow facility with a power of 80%. For this, it was necessary to include 12 patients in each of the treatment groups.<sup>15</sup>

### RESULTS

Figure 1 is a flowchart of the patients during the study. Only one eye per patient was included. Before surgery, no differences in demographic characteristics were found between the two groups (Table 2).

A total of 34 iStents were successfully implanted in 17 patients in group 1. Sixty-two percent (21/34) of the stents were implanted on the first attempt, in 32% (11/34) of the cases a second attempt was required to correctly implant the iStent, a third attempt was needed in 6% (2/34).

Six of the 34 (18%) implanted stents appeared to be malpositioned. Implantation of three stents was too superficial and the stent axis was not parallel to the iris root. One stent was implanted too near to the first stent. One stent was tilted with approximately one third of the proximal end of the stent out of Schlemm's canal; it remained in this position during follow-up. The malposition of the stents was first observed during the first month of follow-up. No further complication occurred during the follow-up for these malpositioned stents. In the sixth case, the stent fell out of the trabecular meshwork during follow-up and remained lodged at the base of the iris. This stent caused no inflammation in the anterior chamber and/or a loss of endothelial cell density higher than expected after cataract surgery during the subsequent postoperative visits.

Before surgery, aqueous flow ( $F$ ; group 1 versus group 2:  $1.78 \pm 0.44 \mu\text{L}/\text{min}$  vs.  $1.74 \pm 0.82 \mu\text{L}/\text{min}$ , respectively,  $P = 0.18$ ; Fig. 2) and outflow facility rates ( $C_T$ ; group 1 versus group 2,  $0.12 \pm 0.03 \mu\text{L}/\text{min}/\text{mm Hg}$  vs.  $0.13 \pm 0.06 \mu\text{L}/\text{min}/\text{mm Hg}$ ;  $P = 0.71$ ) were similar in the two groups (Tables 3, 4). After surgery,  $C_T$  increased in both groups ( $C_T$  at 12 months: group 1:  $0.45 \pm 0.27 \mu\text{L}/\text{min}/\text{mm Hg}$  versus group 2:  $0.19 \pm 0.05 \mu\text{L}/\text{min}/\text{mm Hg}$ ; Fig. 3, Table 3), and increases were significantly greater in group 1 at the 6- and 12-month

TABLE 4. Aqueous Flow

	Group 1		Group 2	
	Mean ± SD	<i>P</i>	Mean ± SD	<i>P</i>
Preoperative	1.78 ± 0.44	0.18*	1.74 ± 0.82	0.18*
1 mo	4.3 ± 1.8	<0.001†	3.9 ± 2.21	0.049†
6 mo	4.05 ± 1.8	0.001†	2.9 ± 1.11	<0.001†
12 mo	2.94 ± 1.52	0.040†	2.12 ± 0.74	0.546†

Data are the mean  $F$  ( $\mu\text{L}/\text{min}$ ) ± SD.

\* Group 1 versus group 2.

† Change with respect to baseline in each group.

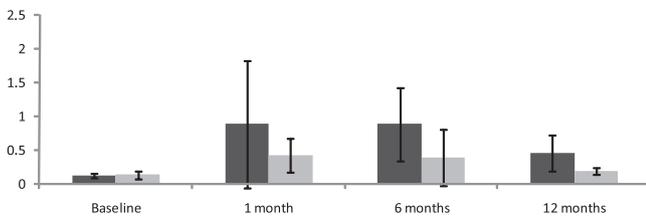


FIGURE 3. Mean trabecular outflow facility ( $C_T$ ) determined by fluorophotometry over the time in groups 1 (black) and 2 (gray).

visits ( $P = 0.04$  and  $P = 0.02$ , respectively). At the end of follow-up (12 months),  $C_T$  was  $0.45 \pm 0.27 \mu\text{L}/\text{min}/\text{mm Hg}$  in group 1 and  $0.19 \pm 0.05 \mu\text{L}/\text{min}/\text{mm Hg}$  in group 2 ( $P = 0.02$ ), representing increases of 275% and 46%, respectively, with no significant changes between the two groups produced in  $F$  ( $P = 0.26$ ).  $F$  at 1 year was  $2.94 \pm 1.52 \mu\text{L}/\text{min}$  in group 1 and  $2.12 \pm 0.74 \mu\text{L}/\text{min}$  in group 2 ( $P = 0.040$  and  $P = 0.546$ , compared with baseline, respectively).

After surgery a statistically significant increase ( $P \leq 0.001$ ) was found in ACV, ACD, and ACA in both groups (Table 5). Statistically significant differences between the ACV, ACD, and ACA values were not seen at 1 and 6 months ( $P > 0.05$ ).

Table 6 summarizes the mean IOP and the mean number of glaucoma medications before and after surgery. Figure 4 shows the IOP over the course of follow-up in the two groups. Both groups started with similar preoperative IOPs ( $P = 0.18$ ). Commencing 1 month after surgery, the IOP reduction was significantly greater in group 1 (1 month:  $8.1 \pm 4.0 \text{ mm Hg}$  vs.  $4.5 \pm 2 \text{ mm Hg}$ ,  $P = 0.04$ ; 3 months:  $9.3 \pm 3.4 \text{ mm Hg}$  vs.  $5.1 \pm 3.1 \text{ mm Hg}$ ,  $P = 0.009$ ; 6 months:  $9.3 \pm 4.1 \text{ mm Hg}$  vs.  $4.3 \pm 3.1 \text{ mm Hg}$ ,  $P = 0.015$ ; and 12 months:  $6.6 \pm 3.0 \text{ mm Hg}$  vs.  $3.9 \pm 2.7 \text{ mm Hg}$ ;  $P = 0.002$ ). The mean number of ocular hypotensive medications required was also significantly less in group 1, 6 months after surgery (Table 6).

Finally, at 12 months, treatment was modified in five patients in group 2 who did not reach their target IOP. Two of the patients were given hypotensive medications, two restarted the ophthalmic medications that they had taken before the study, and one had a selective trabeculoplasty. In group 1, there were no changes in medications for any of the patients.

## DISCUSSION

The presence of the iStent modifies the physiologic dynamic of the aqueous humor flow. Two hypothesis could be formulated. The first possibility is that all the aqueous flow is diverted through the outlets of the stents to flow circumferentially inside Schlemm's canal to the collector channels. The second possibility is that the aqueous flow uses both the stent and the highly resistant trabecular meshwork and inner wall of Schlemm's canal with subsequent limited circumferential flow

through the canal. In both cases, the structural modifications produced by the stents and the changes in the physiological outflow drainage routes could alter the tissues involved in the outflow drainage system. In the 12-month follow-up session, outflow was significantly augmented in group 1. If we consider the increase noted in group 1 and subtract the increase noted in group 2 (that occurred as a result of cataract surgery alone) we can indirectly estimate the increase in the outflow facility due to the implantation of the two stents. We can then deduce that the implantation of the two stents induced a statistically significant increase in the aqueous outflow facility of 157% after 12 months of follow-up. Our results are congruent with the theoretical model developed by Zhou and Smedley,<sup>16</sup> which showed an estimated increase of 146% after the implant of the iStents. Similarly, Bahler et al.<sup>17</sup> reported an 84% increase in the outflow facility after implanting an iStent in normal enucleated eyes. The differences between the findings of these two earlier studies and the present study could be explained by differences in the methods (culture model and in vivo surgery) and by the inclusion in our study of eyes with glaucoma. Inclusion of glaucomatous eyes allows for a potentially greater distortion of the trabecular meshwork and a greater resistance to the aqueous outflow which may, in turn, provide a greater benefit on implanting the stents and overcoming meshwork and juxtacanalicular tissue resistance. Finally, the reduction in outflow facility observed in the group of patients who received the stent may be attributable to either a hypothetical increased resistance at the level of collector channels or to partial obstruction of the stents by inflammatory or pigment precipitates. In the scenario of a partially functioning trabecular meshwork, the reduced trabecular outflow facility may be attributable to both disease progression with increased resistance of juxtacanalicular tissue or/and to the partial obstruction of the stent.

Frequently, after microbypass implantation, a small blood reflux is observed through the stent, which positively indicates the correct placement of the implant within Schlemm's canal. Adequate surgical management of the reflux by rinsing and refilling of the chamber with viscoelastic to create tamponade should allow suitable visualization to implant the second stent uneventfully. In fact, improper positioning of several stents was probably due to decreased visualization because of blood reflux into the anterior chamber after the first implantation. Carefully rinsing the blood reflux before implanting the second stent and ensuring that the two stents are placed far enough apart would probably have reduced the chances that the second stent would be malpositioned. Although the IOP and fluorophotometry results were analyzed in the patients with both stents implanted correctly versus one implanted correctly, no differences were found between the two groups, perhaps because of the low number of patients.

The effect of cataract surgery on the aqueous outflow facility has been documented by various authors. Meyer et al.<sup>18</sup>

TABLE 5. Changes in the Anterior Chamber Induced by Cataract Surgery

	ACV (mm <sup>3</sup> )			ACD (mm)			ACA (deg)		
	Preop	1 mo	6 mo	Preop	1 mo	6 mo	Preop	1 mo	6 mo
Group 1	150 ± 33	192 ± 32	198 ± 30	2.8 ± 0.3	3.5 ± 0.5	3.3 ± 0.3	34.3 ± 3	47 ± 4	49 ± 4
Group 2	152 ± 20	200 ± 22	198 ± 18	3 ± 0.2	3.8 ± 0.7	3.6 ± 0.7	34.6 ± 4	47 ± 4	47 ± 5
All subjects	151 ± 29	201 ± 25	198 ± 31	3 ± 0.3	3.6 ± 0.6	3.4 ± 0.5	35 ± 3.1	47.4 ± 4	49.5 ± 5
<i>P</i>	—	0.000*	0.001†	—	0.002	0.000	—	0.000	0.000

Data are expressed as the mean ± SD.

\* Month 1 versus baseline.

† Month 6 versus baseline.

TABLE 6. Intraocular Pressure and Number of Ocular Hypotensive Medications

	IOP			Medications		
	Group 1	Group 2	<i>P</i> *	Group 1	Group 2	<i>P</i> †
Preoperative baseline‡	24.2 ± 1.8	23.6 ± 1.5	0.18	1.1 ± 0.5 (0-1)/1	1.2 ± 0.7 (0-2)/1	0.66
1 day	21.9 ± 10.1	26.4 ± 8.1	0.08	—	—	—
1 to 2 wk	16.5 ± 4.4	18.2 ± 4.2	0.28	—	—	—
1 mo	16.7 ± 3.1	18.9 ± 1.4	0.01	0.1 ± 0.2 (0-1)/0	0.1 ± 0.3 (0-1)/0	0.51
3 mo	15.2 ± 2.5	18.6 ± 3.4	0.009	0.1 ± 0.2 (0-1)/0	0.3 ± 0.5 (0-1)/0.5	0.06
6 mo	15.6 ± 3.3	19.6 ± 4	0.02	0.1 ± 0.5 (0-2)/0	0.5 ± 0.7 (0-2)/0.5	0.03
12 mo	17.6 ± 2.8	19.8 ± 2.3	0.04	0.00 (0)/0	0.7 ± 1.0 (0-3)/2	0.007

IOP is expressed as mean mm Hg ± SD; and the number of hypotensive medications is expressed as the mean ± SD (range)/median.

\* Mean IOP comparison between groups.

† Glaucoma medication comparison between groups.

‡ Preoperative baseline IOP after washout period.

found, through tonography, a 71% increase in normal patients undergoing phacoemulsification. We noted an increase in group 2 (patients only having cataract surgery) of 46% from baseline values. Once again, the distinct characteristics of study populations (normal versus glaucomatous) could explain the differences found, assuming a smaller increase in the outflow facility in glaucoma patients due to lower functionality and the structural changes in their trabecular meshwork.<sup>19-22</sup>

With respect to efficacy, the iStent in combination with cataract surgery provided significant IOP reductions as well as a significant reduction in the need for concomitant medical treatment. Conversely, the mean IOP in group 2 was close to 20 mm Hg, suggesting that more medications should have been introduced over the course of follow-up to keep the IOP at a lower level in the cataract-only group.

There was a gradual increase in concomitant medications in group 2 at each planned study visit. In fact, in the last visit, five patients in group 2 were given additional medications, compared with none in group 1.

From the initial high postoperative values in the fluorophotometry study, we observed a decrease in *F* and *C<sub>T</sub>* in both groups during the follow-up. Cataract surgery caused changes to the anterior chamber in both groups that were taken into account in the postoperative fluorophotometry calculations. However, these changes are still a limitation of the study. These changes and the postoperative alteration of the hematoaqueous barrier could bias the measurements, especially during the first follow-up months.<sup>23</sup> For this reason, the values obtained from the control group add a crucial perspective. In addition, the reduction in outflow facility observed in the group of patients who received the stent may be attributable to

either a hypothetical increased resistance at the level of collector channels or to partial obstruction of the stents by inflammatory or pigment precipitates. In the scenario of a partially functioning trabecular meshwork, the reduced trabecular outflow facility may be attributable to both disease progression with increased resistance of juxtacanalicular tissue and/or to the partial obstruction of the stent.

Bahler et al.<sup>17</sup> found similar results when implanting iStents in normal enucleated eyes (IOP reductions of 9 mm Hg or 45% from baseline values). At 6 months, Spiegel et al.<sup>24</sup> reported an IOP decrease of 5.7 mm Hg from treated baseline and a decrease in the number of drugs from 1.5 to 0.5 after combined cataract surgery and the implantation of one stent. The implantation of two iStents could explain the improved results in our study. In a similar population of patients who are nonresponsive to glaucoma treatment and who had cataract surgery and one iStent, Martinez de-la-Casa et al. described decreases of 6 mm Hg (25%) at 6 months of follow-up and 4.4 mm Hg (18.3%) at 1 year, with 1.2 fewer medications (*P* < 0.0001) at 12 months (Martinez-de-la-Casa JM, et al. *IOVS* 2007;48:ARVO E-Abstract 824).

Several publications show that cataract surgery could play a role in lowering IOP as observed in group 1. Even though it has only been demonstrated with grade C scientific evidence,<sup>25</sup> the IOP decrease after isolated cataract surgery in patients with POAG is estimated to be between 2 and 4 mm Hg.<sup>26,27</sup> In patients with POAG at 1 year after cataract surgery, Merkur et al.<sup>18</sup> found pressure reductions of 1.9 mm Hg (11.5%); Shingleton et al.<sup>28</sup> reported reductions of 1.9 mm Hg (6.5%); Tong and Miller<sup>29</sup> found IOP reductions of 2.3 mm Hg (decrease of 13%); and Hayashi et al.<sup>30</sup> reported IOP reductions of 4.3 ± 4.2 mm Hg (21%). Pöhljalainen et al.<sup>31</sup> reported a mean drop in intraocular pressure of 3.3 mm Hg after 3 years of follow-up in patients with open-angle glaucoma undergoing cataract extraction by phacoemulsification.

In this study, we found a pressure decrease in group 2 from preoperative baseline IOP of 3.9 mm Hg (16.3%), which could be related to the 46% increase in *C<sub>T</sub>* found 1 year after the cataract surgery. The opening of the iridocorneal angle and the increase in ACV after cataract surgery could partly explain this increase in *C<sub>T</sub>* (albeit probably transient) in patients with POAG and OHT.<sup>32</sup> In our study, we noted a significant increase in iridocorneal angle opening and in the volume and depth of the anterior chamber, similar to those reported by other authors.<sup>29,33</sup>

The results of this study demonstrate that the iStent, in combination with cataract surgery, induces a significant increase in the aqueous outflow facility that translates into a significant decrease in IOP in patients with POAG. These re-

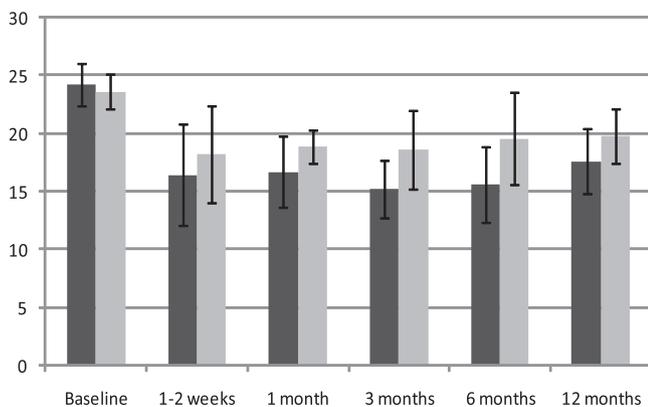


FIGURE 4. Intraocular pressure evolution during the follow-up in groups 1 (black) and 2 (gray).

sults are compelling in the context of historical control and observational and theoretical models, even in light of the complexity of aqueous humor dynamics in vivo and the imprecision of existing diagnostic techniques.

Our findings suggest that the iStent may play an increasingly meaningful clinical role in the management of OAG patients. Future studies with a greater number of patients and longer term follow-up are needed to confirm these results.

## References

- Grant WM. Experimental aqueous perfusion in enucleated human eyes. *Arch Ophthalmol*. 1963;69:783-801.
- Ethier CR, Kamm RD, Palaszewski BA, Johnson MC, Richardson TM. Calculations of flow resistance in the juxtacanalicular meshwork. *Invest Ophthalmol Vis Sci*. 1986;27:1741-1750.
- Gonzalez de la Rosa M, Gonzalez-Hernandez M, Garcia Feijoo J, Morales J, Azuara-Blanco A. Diagnostic accuracy and reproducibility of tendency oriented perimetry in glaucoma. *Eur J Ophthalmol*. 2006;16:259-267.
- Gonzalez de la Rosa M, Gonzalez-Hernandez M, Diaz Aleman T, Sanchez Mendez M. Stabilization and comparison of TOP and bracketing perimetric strategies using a threshold spatial filter. *Graefes Arch Clin Exp Ophthalmol*. 2007;245:1303-1309.
- Gonzalez-Hernandez M, Morales J, Azuara-Blanco A, Sanchez JG, de la Rosa MG. Comparison of diagnostic ability between a fast strategy, tendency-oriented perimetry, and the standard bracketing strategy. *Ophthalmologica*. 2005;219:373-378.
- Mills RP, Budenz DL, Lee PP, et al. Categorizing the stage of glaucoma from pre-diagnosis to end-stage disease. *Am J Ophthalmol*. 2006;141:24-30.
- Zeyen T, Roche M, Brigatti L, Caprioli J. Formulas for conversion between Octopus and Humphrey threshold values and indices. *Graefes Arch Clin Exp Ophthalmol*. 1995;233:627-634.
- Beneyto Martin P, Fernández Vila TM, Pérez Martínez TM, Aliseda Pérez D. A fluorophotometric study on the aqueous humor dynamics in primary open angle glaucoma. *Int Ophthalmol*. 1992;16:311-314.
- Beneyto Martin P, Fernández Vila TM, Pérez Martínez TM, Aliseda Pérez D. Determination of the pseudofacility by fluorophotometry in the human eye. *Int Ophthalmol*. 1996;19:219-223.
- Jones RF, Maurice MD. New methods of measuring the rate of aqueous flow in man with fluorescein. *Exp Eye Res*. 1966;5:208-220.
- Yablonski ME, Zimmerman TJ, Waltman SR, et al. A fluorophotometric study of the effect of topical timolol on aqueous humor dynamics. *Exp Eye Res*. 1978;27:135-142.
- Anders Bill, Calbert I Phillips. Uveoscleral drainage of aqueous humour in human eyes. *Exp Eye Res*. 1971;12:275-281.
- Goldmann H. Über fluorescein in der menschlichen Vorderkammer. Das Kammerwasser-Minutenvolumen des Menschen. *Ophthalmologica*. 1950;119:65.
- Phelps C, Armaly MF. Measurement of episcleral venous pressure. *Am J Ophthalmol*. 1978;85:35-42.
- Dinslage S, Hueber A, Diestelhorst M, Krieglstein G. The influence of Latanoprost 0.005% on aqueous humor flow and outflow facility in glaucoma patients: a double-masked placebo controlled clinical study. *Graefes Arch Clin Exp Ophthalmol*. 2004;242(8):654-660.
- Zhou J, Smedley G. A trabecular bypass flow hypothesis. *J Glaucoma*. 2005;14:74-83.
- Bahler CK, Smedley GT, Zhou J, Johnson DH. Trabecular bypass stents decrease intraocular pressure in cultured human anterior segments. *Am J Ophthalmol*. 2004;138:988-994.
- Meyer MA, Savitt ML, Kopitas E. The effect of phacoemulsification on aqueous outflow facility. *Ophthalmology*. 1997;104:1221-1227.
- Lütjen-Drecoll E, Futa R, Rohen JW. Ultra histochemical studies on tangential sections of the trabecular meshwork in normal and glaucomatous eyes. *Invest Ophthalmol Vis Sci*. 1981;21:563-573.
- Alvarado JA, Murphy CG. Outflow obstruction in pigmentary and primary open angle glaucoma. *Arch Ophthalmol*. 1992;110:1769-1778.
- Rohen JW, Lütjen-Drecoll E, Flügel C, Meyer M, Grierson I. Ultrastructure of the trabecular meshwork in untreated cases of primary open-angle glaucoma (POAG). *Exp Eye Res*. 1993;56:683-692.
- Tektas Ozan-Yü, Lütjen-Drecoll E. Structural changes of the trabecular meshwork in different kinds of glaucoma. *Exp Eye Res*. 2009;88(4):769-775.
- Shah SM, Spalton DJ, Allen RJ, Smith SE. A comparison of the laser flare cell meter and fluorophotometry in assessment of the blood-aqueous barrier. *Invest Ophthalmol Vis Sci*. 1993;34:3124-3130.
- Spiegel D, García Feijoo J, García Sánchez J, Lamielle H. Coexistent primary open-angle glaucoma and cataract: preliminary analysis of treatment by cataract surgery and the iStent trabecular micro-bypass stent. *Adv Ther*. 2008;25(5):453-464.
- Friedman DS, Jampel HD, Levkovitch-Verbin H, Robinson KA, Bass EB. Surgical strategies for coexisting glaucoma and cataract: an evidence-based update. *Ophthalmology*. 2002;109:1902-1913.
- Merkur A, Damji KF, Mintsoulis G, Hodge WG. Intraocular pressure decrease after phacoemulsification in patients with pseudoexfoliation syndrome. *J Cataract Refract Surg*. 2001;27:528-532.
- Suzuki R, Kuroki S, Fujiwara N. Ten-year follow-up of intraocular pressure after phacoemulsification and aspiration with intraocular lens implantation performed by the same surgeon. *Ophthalmologica*. 1997;211:79-83.
- Shingleton BJ, Gamell LS, O'Donoghue MW, et al. Long-term changes in intraocular pressure after clear corneal phacoemulsification: normal patients versus glaucoma suspect and glaucoma patients. *J Cataract Refract Surg*. 1999;25:885-890.
- Tong JT, Miller KM. Intraocular pressure change after sutureless phacoemulsification and foldable posterior chamber lens implantation. *J Cataract Refract Surg*. 1998;24:256-262.
- Hayashi K, Hayashi H, Nakao F, Hayashi F. Effect of cataract surgery on intraocular pressure control in glaucoma patients. *J Cataract Refract Surg*. 2001;27:1779-1786.
- Pohjalainen T, Vesti E, Risto J, Uusilato RJ, Laatikainen L. Phacoemulsification and intraocular lens implantation in eyes with open angle glaucoma. *Acta Ophthalmol Scand*. 2001;79:313-316.
- Hayashi K, Hayashi H, Nakao F, et al. Changes in anterior chamber angle width and depth after intraocular lens implantation in eyes with glaucoma. *Ophthalmology*. 2000;107:698-703.
- Nemeth G, Vajas A, Kolozsvari B, et al. Anterior chamber depth measurements in phakic and pseudophakic eyes: Pentacam versus ultrasound device. *J Cataract Refract Surg*. 2006;32:1331-1335.