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A Randomized Trial of a Schlemm's Canal Microstent with Phacoemulsification for Reducing Intraocular Pressure in Open-Angle Glaucoma

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Abstract

Purpose: To assess the safety and effectiveness of the Hydrus Microstent (Ivantis, Inc, Irvine, CA) with concurrent cataract surgery (CS) for reducing intraocular pressure (IOP) in open-angle glaucoma (OAG).

Design: Prospective, multicenter, randomized, single-masked, controlled clinical trial.

Participants: One hundred eyes from 100 patients 21 to 80 years of age with OAG and cataract with IOP of 24 mmHg or less with 4 or fewer hypotensive medications and a washed-out diurnal IOP (DIOP) of 21 to 36 mmHg.

Methods: On the day of surgery, patients were randomized 1:1 to undergo CS with the microstent or CS alone. Postoperative follow-up was at 1 day, 1 week, and 1, 3, 6, 12, 18, and 24 months. Washout of hypotensive medications was repeated at 12 and 24 months.

Main Outcome Measures: Response to treatment was defined as a 20% or more decrease in washed out DIOP at 12 and 24 months of follow-up compared with baseline. Mean DIOP at 12 and 24 months, the proportion of subjects requiring medications at follow-up, and the mean number of medications were analyzed. Safety measures included change in visual acuity, slit-lamp observations, and adverse events.

Results: The proportion of patients with a 20% reduction in washed out DIOP was significantly higher in the Hydrus plus CS group at 24 months compared with the CS group (80% vs. 46%; P ¼ 0.0008). Washed out mean DIOP in the Hydrus plus CS group was significantly lower at 24 months compared with the CS group (16.93.3 mmHg vs. 19.24.7 mmHg; P ¼ 0.0093), and the proportion of patients using no hypotensive medications was significantly higher at 24 months in the Hydrus plus CS group (73% vs. 38%; P ¼ 0.0008). There were no differences in follow-up visual acuity between groups. The only notable device-related adverse event was focal peripheral anterior synechiae (1e2 mm in length). Otherwise, adverse event frequency was similar in the 2 groups.

Conclusions: Intraocular pressure was clinically and statistically significantly lower at 2 years in the Hydrus plus CS group compared with the CS alone group, with no differences in safety.

Abbreviations and Acronyms

AMD age-related macular degeneration, BCVAbest-correct visual acuity, CS cataract surgery; DIOP diurnal intraocular pressure; IOL intraocular lens; IO Pintraocular pressure; MIG; Smicroinvasive glaucoma surgery; OA; Gopen-angle glaucoma; OHTS Ocular Hypertension Treatment Study; PAS peripheral anterior synechiae; PSD pattern standard deviation

Introduction

Glaucoma remains the second leading cause of blindness worldwide.[1] Elevated intraocular pressure (IOP) is an important risk factor for the progression of the disease. It can be lowered medically or surgically depending on severity and progression.[2, 3] Control of IOP has been shown to reduce glaucoma progression and the resultant visual field loss.[4, 5] Topical medications have a proven record of efficacy and safety, but they are accompanied by side effects such as exacerbation of dry eye and ocular surface disease[6] and present clinical limitations related to compliance and adherence.[7, 8, 9] Furthermore, chronic medication use may reduce the success rate of subsequent glaucoma filtration surgery.[10]

A new class of microinvasive glaucoma surgery (MIGS) devices[11] has been developed that do not require scleral incisions and increase outflow by directly accessing Schlemm's canal[12] or by shunting fluid from the anterior chamber to the suprachoroidal[13] or subconjunctival[14] space. Because MIGS devices are placed ab interno using the same clear corneal incision created for phacoemulsification, they are readily combined with cataract surgery (CS). Microinvasive glaucoma surgery approaches could avoid complications of traditional glaucoma surgery,[15] such as hypotony and bleb revision, and may provide an option for treatment of mild as well as more advanced disease.

The purpose of the HYDRUS II study was to evaluate clinically a new Schlemm's canal scaffold (Hydrus Microstent; Ivantis, Inc, Irvine, CA) for IOP reduction after concomitant CS. The Hydrus Microstent is an 8-mm long crescent-shaped open structure, curved to match the shape of Schlemm's canal. The microstent is implanted ab interno through a clear corneal incision into Schlemm's canal using a preloaded hand-held injector. After being implanted, the microstent bypasses the trabecular meshwork and dilates Schlemm's canal over 3 clock hours to provide direct aqueous access from the anterior chamber to multiple collector channels (Fig 1) without interfering with or damaging the structures.[16]

Methods

Study Design

The HYDRUS II study was a prospective, single-masked, randomized, controlled clinical trial conducted at 7 European investigational sites (see listing of authors institutional affiliations). The study protocol was approved by the medical ethics committee at each site and conducted according the principals described in the Declaration of Helsinki. All study subjects provided written informed consent before commencing participation in the trial. Patients from the participating centers with concurrent open-angle glaucoma and cataract who met the study entry criteria were assigned randomly in a 1:1 ratio according to a computer-generated listing just before surgery to undergo either CS (phacoemulsification and intraocular lens [IOL] implantation) with the Hydrus Microstent (Hydrus plus CS group) or CS alone (CS group). Subjects were followed up for 2 years, at which time the efficacy and safety end points were ascertained. Subjects remained masked to treatment assignment for the course of the study.

The study was designed by the first and last authors and the sponsor (Ivantis, Inc) in accordance with the study design recommendations described in the American National Standards Institute guidance for glaucoma aqueous shunts.[17] The study was registered in the National Library of Medicine database (clinicaltrials.gov identifier, NCT01818115). The data were 100% source document verified by independent monitors (MediTech Strategic Consultants BV, Vaals, The Netherlands) with funding provided by the sponsor. The analyses were conducted by the sponsor.

Study Patients

Patients with concurrent cataract and open-angle glaucoma were enrolled prospectively in the study. Only 1 eye per patient was eligible for treatment, although both eyes could be screened for inclusion. The study eye was required to have an IOP of 24 mmHg or less with no more than 4 hypotensive medications, Shaffer grade III or IV chamber angle in all quadrants, and Humphrey (Carl Zeiss, Jena, Germany) visual field changes characteristic of glaucoma or glaucomatous optic nerve damage confirmed by ophthalmoscopy and nerve fiber layer imaging. Glaucoma severity was limited to subjects considered capable of safely undergoing medication washout. Before surgery, subjects were washed out of all hypotensive medications in the study eye for a variable period, depending on the class of medication in use at the time of screening. The washout protocol is described in the Ocular Hypertension Treatment Study.[18] At the completion of the washout, a preoperative baseline diurnal IOP (DIOP) value was obtained by averaging 3 Goldmann tonometry measurements obtained 4 hours apart between 8AM and 4PM. The tonometry protocol used a 2-person system (an observer and a reader), and 2 readings were obtained at each time point during the day. If the difference in the 2 measurements was more than 2 mmHg, a third measurement was obtained. The average of 2 measurements or the median value of 3 was used for the time point, and the average of the IOP measurements at all 3 time points was the mean DIOP. The DIOP value was required to be between 21 and 36 mmHg for study inclusion. Clinical exclusion criteria included angle-closure glaucoma, secondary glaucomas except pseudoexfoliation or pigment dispersion syndromes, exudative age-related macular degeneration (AMD), proliferative diabetic retinopathy, or significant risk of glaucomatous vision loss because of washout of IOP-lowering medications. Anatomic exclusion criteria were narrow angle or other angle abnormality visible on gonioscopy, central corneal thickness of less than 480 μm or more than 620 μm, or clinically significant corneal dystrophy. Patients with prior corneal surgery, argon laser trabeculoplasty, cycloablation, or any incisional glaucoma procedure, such as trabeculectomy, tube shunts, deep sclerectomy, or canaloplasty, also were excluded.

Study Device

The microstent is made from nitinol (nickel–titanium alloy), a material with unique shape memory properties that has been used widely in vascular and other medical applications.19, 20, 21 The biocompatibility of nitinol for ocular applications has been reported previously,[22] and the Hydrus Microstent has been evaluated in rabbit and primate ocular models.[23] Multiple laboratory studies examining the Hydrus Microstent using human cadaveric tissue in an anterior segment perfusion model have demonstrated an increase in outflow facility compared with untreated controls.24, 25

Study Treatment

Patients were administered preoperative medications according to the standard practice of each site for CS. All patients underwent CS with phacoemulsification through a clear corneal or limbal incision. Patients randomized to the Hydrus plus CS group had the microscope repositioned and the head tilted to allow a clear view of the angle structures with a gonioprism. Additional viscoelastic was introduced for chamber maintenance and better angle visualization. Miotics were administered at the surgeon's discretion. The Hydrus delivery cannula was inserted through the same incision used for the CS or through a 1- to 1.5-mm secondary incision when the view of the anterior chamber angle was not optimal or if the target implantation site could not be accessed with the cataract incisions. The beveled tip of the cannula was used to perforate the trabecular meshwork, and the microstent was implanted into Schlemm's canal by rotating the advancement mechanism with the index finger, leaving 1 to 2 mm (the inlet segment) remaining in the anterior chamber. If necessary, the microstent could be retracted and reinserted in a different location. On confirmation of position in the canal, the delivery system was withdrawn and the viscoelastic removed; the anterior chamber was inflated with balanced salt solution to achieve physiologic IOP. Postoperative care included a topical antibiotic for 4 to 7 days and a tapering dose of a topical corticosteroid for up to 4 weeks.

Follow-up Examinations

Follow-up examinations were conducted per protocol at 1 day, 1 week, and 1, 3, 6, 12, 18, and 24 months. Interim visits were conducted at any time at the discretion of the treating physician. At all scheduled visits, the examination included slit-lamp biomicroscopy, ophthalmoscopy, manifest refraction, best-correct visual acuity (BCVA) assessment using the Early Treatment of Diabetic Retinopathy Study system, and measurement of IOP using Goldmann applanation tonometry. A Humphrey 24-2 Swedish interactive threshold algorithm standard visual field was performed at 3, 6, 12, 18, and 24 months. Ocular hypotensive medications could be reintroduced if follow-up IOP exceeded 19 mmHg or at any IOP level with evidence of progression of optic nerve damage or visual field loss. For subjects taking hypotensive medications at 12 and 24 months, a safety visit was conducted with IOP measurement before instructing the patient to cease hypotensive medications in the study eye, and the DIOP was measured according to the same washout schedule as the baseline visit.

End Points

The primary efficacy end point was the proportion of patients with a 20% or more reduction in mean washed out DIOP in the Hydrus plus CS group as compared with the CS group. Additional outcome measures included the mean washed out DIOP, the proportion of patients taking ocular hypotensive medications, and medication use throughout the follow-up period. Safety end points were intraoperative complications, the observed rate of ocular adverse events, loss of visual acuity, and ocular health over the follow-up period.

Statistical Analysis

This trial was powered to detect a difference in mean DIOP between groups of 3 mmHg at 2 years of follow-up. With study power of 80%, a 2-sided significance level of 0.05, and a 1:1 randomization ratio, 78 patients were required for the study. After accounting for 10% attrition per year for the 2-year course of the study, a sample size of 100 patients was selected for the study. A difference of 3 mmHg was considered a clinically meaningful IOP reduction on the basis of observed decreases in progression for each 1 mmHg with pharmacologic therapy in a previous study.[26]
The analyses for the primary end point were performed on the basis of the intention-to-treat principle. Means and standard deviations of continuous variables are presented according to treatment group. Within-group and between-group differences were tested using unpaired *t* tests. For categorical variables, counts and percentages are presented according to treatment group; outcome values were tested using the Fisher exact test for binary variables. Exited patients or patients who could not complete follow-up washout for safety reasons or who underwent glaucoma surgery of any kind were defined as failures for the purpose of the primary end point. Analyses of variable data were performed using available data.

Results

Characteristics of the Study Patients

A total of 100 eyes from 100 patients (50 per treatment arm) were randomized into the study from July 2011 through April 2012 from 7 sites in Germany, Spain, The Netherlands, and Italy. Baseline characteristics for study subjects are shown in Table 1. The study population was almost completely white owing to the geography of the study sites. Baseline characteristics were similar for both groups; there were no statistically significant differences in age, gender, BCVA, or glaucoma risk factors (visual field pattern standard deviation, medication use, or IOP before or after washout). Primary open-angle glaucoma was the predominant diagnosis. There was a broad range of glaucoma severity, as defined by the visual field mean deviation and pattern standard deviation in both groups. At the screening visit, the mean IOP was 18.9±3.3 mmHg and 18.6±3.8 mmHg with a mean of 2.0±1.0 and 2.0±1.1 medications in the Hydrus plus CS and CS groups, respectively (mean ± standard deviation, see the Statistical Analysis subsection within "Methods"). The most frequently used medications were prostaglandin analogs (78%) and β-blockers (60%), or a combination of both. After completion of medication washout, the DIOP was 26.3±4.4 mmHg and 26.6±4.2 mmHg in the Hydrus plus CS and CS groups, respectively.

Microstent Implantation

Microstent implantation was successful in 48 (96%) of 50 procedures. The microstent was implanted in the nasal hemisphere in 43 of 48 cases and in the inferior temporal quadrant for the other 5 subjects. There were no instances of lost or migrating microstents or of corneal or iris touch. One of the unsuccessful implantation procedures was the result of excessive eye movement possibly related to inadequate anesthesia. The second was the result of hyphema, which led to an obscured gonioscopic view, precluding a second attempt. Both of these patients were followed up for the duration of the study and remained in the intention-to-treat population.

Follow-up Visits

Figure 2 shows the patient flow from randomization through 2 years of follow-up. Before the 12-month visit, 2 patients from the Hydrus plus CS group and 1 patient from the CS group exited the study for non–health-related reasons, for a 12-month subject accountability rate of 97 (97%) of 100. Between 12 and 24 months, 4 additional patients exited from the study: 1 patient died of cardiac disease, 1 patient developed lung cancer, 1 declined further participation after secondary glaucoma surgery, and 1 patient was lost to follow-up, all in the CS group, for a 24-month accountability rate of 93 (93%) of 100.

In addition to the patients who exited the study, some patients did not undergo washout of hypotensive medications at the designated follow-up visit, primarily because of safety concerns related to uncontrolled IOP, advancing visual field loss or split fixation, or optic disc hemorrhage. At 12 months, a total of 5 subjects did not undergo washout (2 from the Hydrus plus CS group and 3 from the CS group). Another 2 patients from the CS group came to the clinic for the prewashout safety visit, but did not return for the DIOP measurements. Thus, the total number of evaluable washed out subjects at 12 months was 90 (93%) of 97. At month 24, a total of 11 subjects did not undergo washout for safety reasons, 3 from the Hydrus plus CS group and 8 from the CS group. In addition, 1 patient from the control group did not return for a washout DIOP measurement after the 24-month visit. Between 12 and 24 months, 1 subject in the Hydrus plus CS group and 2 from the CS group had secondary glaucoma surgery and were no longer candidates for washout. Thus at 24 months, the total number of evaluable washout subjects was 78 (87%) of 90.

Effectiveness Measurements

The results for the primary effectiveness end point are shown in Figure 3. At 24 months, the proportion of patients with a 20% or more reduction in washed out DIOP compared with baseline was 80% (40/50) in the Hydrus plus CS group compared with 46% (23/50) in the CS group (95% confidence interval, 16.3%–51.7%; $P = 0.0008$). Figure 4 shows the mean washed out DIOP for both study groups at baseline, 12, and 24 months. In the Hydrus plus CS group, the mean washed out DIOP was 16.6±2.8 mmHg at 12 months and 16.9±3.3 mmHg at 24 months. In comparison, the mean washed out DIOP in the CS group was 17.4±3.7 mmHg and 19.2±4.7 mmHg at the same follow-up time points. Follow-up mean washed out DIOP was significantly lower than baseline DIOP in both groups at 12 and 24 months. However, at 24 months, the mean washed out DIOP in the Hydrus plus CS group was significantly lower compared with the CS group (16.9±3.3 mmHg vs. 19.2±4.7 mmHg; $P = 0.0093$).

Figures 5 and 6 show the IOP and medication use at each visit throughout the study. There was a significantly higher incidence of elevated IOP on the first day after surgery in the CS group. An IOP of 35 mmHg or more was observed in 26% (13/50) of CS eyes compared with 10% (5/50) in the Hydrus plus CS group. After the first postoperative day, patients with elevated IOP were remedicated, and effectiveness of the treatment was reflected in the use of medications throughout the remainder of the study until washout. Compared with the preoperative medicated IOP of 18.6 to 18.9 mmHg, the mean medicated IOP was between 16 and 17 mmHg in both groups from month 3 throughout the remainder of the follow-up period, although this was accomplished with increased medication use in the CS group. By 24 months, 0.5±1.0 medication per patient was used in the Hydrus plus CS group compared with 1.0±1.0 in the CS group ($P = 0.0189$). At 24 months, the proportion of patients using 2 or more medications in the CS group was 27% versus 15% in the Hydrus plus CS group ($P = 0.1996$). As shown in Figure 7, the ratio of unmedicated patients increased in favor of the Hydrus plus CS group throughout the follow-up period. By 24 months, the difference was almost 2:1 (72.9% vs. 37.8%; $P = 0.0008$).

Safety Measurements

Ophthalmic findings in the first postoperative month included routine slit-lamp and fundus observations and were similar in both groups. Anterior segment inflammation indicated by cells and flare were noted at 1 week but were largely absent at 1 month. The corneal stroma was normal by 1 month in all patients; however, Descemet folds were noted in 1 patient in each group at the 1-month visit, but both resolved by the 3-month visit. Iris erosion was noted in 3 CS subjects at 1 month and none in the Hydrus plus CS group. The BCVA decreased by 2 lines in 2 patients in the Hydrus plus CS group, but resolved by 1 month. There were no significant differences in BCVA between groups throughout the remainder of follow-up. Most patients in both groups showed an increase in BCVA of 2 lines or more, although there was 1 patient with persistent BCVA loss of more than 2 lines in the CS arm throughout the follow-up period. By month 3, BCVA was 20/40 or better in 96% of Hydrus plus CS subjects and 90% of CS subjects.

Table 2 shows the ocular adverse events observed in the study. There were few serious adverse events in study eyes from either group, and no reports of hypotony or microstent migration or dislocation in the Hydrus plus CS group. Three subjects underwent glaucoma surgery during the second year of follow-up, 2 in the CS group and 1 in the Hydrus plus CS group, for elevated IOP despite maximum tolerated medical therapy. There was a significant increase in the rate of peripheral anterior synechiae (PAS) formation in the Hydrus plus CS group at the 2-year follow-up ($P = 0.0077$), typically manifested as focal iris tissue adhesion to the device or chamber angle of less than 1 clock hour located at or near the inlet segment of the microstent. The device inlet projects approximately 1 mm into the anterior chamber and is the primary channel of aqueous flow based on in vitro outflow analysis, which may account for the tissue response. The presence of PAS had no apparent effect on the study outcomes, because the IOP and medication use in patients with observed PAS were similar to those found in the overall Hydrus plus CS group.

Discussion

This randomized, controlled, single-masked trial demonstrated a clear benefit of concurrent implantation of a new Schlemm's canal microstent with CS for reducing IOP and medication use in open-angle glaucoma during 2 years of follow-up when compared with CS alone. The 12-month postoperative findings from this study support published data for the effectiveness of a Schlemm's canal implant during CS.[27, 28] The durability of the IOP-lowering effect with microstent implantation from year 1 to year 2 in this study is a novel finding for a MIGS device. There is only 1 previously conducted 2-year controlled, randomized study for a MIGS device, and the reported efficacy at 2 years is contradictory, depending on how the analysis was performed.[29, 30]
Current glaucoma therapy includes several methods, such as medications, laser, and incisional surgery, all aimed at lowering IOP, and often patients will need more than 1 of these treatments. The concomitant application of these different therapies in clinical studies frequently confounds interpretation of results. This study incorporates the recent recommendations from the American National Standards Institute Z80.27 Committee aimed at reducing the effect of confounding factors and bias in the clinical evaluation of new glaucoma devices. Key among the recommendations included in this study were the use of medication washout both at enrollment and at annual follow-up, DIOP rather than single measurements, masking of the tonometer reader, and a second year of follow-up. Accordingly, the HYDRUS II trial is the first study to report an IOP reduction related to a MIGS device without the influence of concomitant ocular hypotensive medications.

A 20% or more drop in IOP is categorized by the American Academy of Ophthalmology as a level A therapeutic recommendation[2] for the treatment of glaucoma. In the HYDRUS II study, the Hydrus plus CS group met this objective without medications in 80% of patients at the 24-month follow-up. This outcome was supported by other study findings, such as a significant drop in mean washed out

DIOP, stability in the mean washed out DIOP from year 1 to year 2, and a persistent reduction in medication use throughout the course of follow-up.
Additionally, the control group of this study is the first report in a multicenter, randomized trial on the effect of phacoemulsification in open-angle glaucoma with a provision for washout of medications at follow-up. The observed reduction in DIOP in the CS group was approximately 9 mmHg at 1 year and 7.5 mmHg at 2 years. Both values are significantly greater than those reported in prior studies. In the HYDRUS II study design, the effect of phacoemulsification was estimated based on previous reports suggesting a decrease in IOP of approximately 5 mmHg.31, 32, 33 This difference may be explained because of the confounding effect of medications and the retrospective nature of the previous studies.
The only prior longitudinal study to assess the IOP-lowering effect of phacoemulsification without the confounding effect of medications is the Ocular Hypertension Treatment Study (OHTS), where the subgroup of patients from the observation arm undergoing CS were evaluated compared with the untreated cohort. An initial IOP reduction of 4 mmHg was observed in the first year, and although it diminished over time, it remained significantly lower than the reference group for 3 years.[34]
Several further factors in this HYDRUS II study may account for the difference in magnitude of the effect of phacoemulsification on IOP compared with previous reports in general and OHTS in particular. First, the preoperative IOP in the phacoemulsification group was 26.6±4.4 mmHg in HYDRUS II compared with 23.9±3.2 mmHg in OHTS. Intraocular pressure reduction after phacoemulsification has been shown to be proportional to preoperative IOP, with significantly greater IOP reduction observed among those with higher preoperative IOP.[35] Additionally, the HYDRUS II study excluded patients with baseline IOP of less than 21 mmHg, whereas the OHTS CS subgroup had no minimum IOP for inclusion. Regression to the mean is another factor that can influence data interpretation for a physiologic parameter known to fluctuate like IOP. Although the baseline DIOP for HYDRUS II was obtained on a single day, the OHTS study baseline was the average of IOP measurements obtained over 3 previous visits. Averaging measurements obtained over several days has been shown to reduce regression to the mean.[36] Finally, the HYDRUS II study did not include patients with ocular hypertension, eligible patients had to have documented optic nerve damage characteristic of glaucoma. Taken together, these factors could account for the magnitude of the IOP-lowering effect of phacoemulsification in HYDRUS II compared with that reported for the OHTS subgroup.
The mean DIOP in the Hydrus plus CS arm was significantly lower compared with the CS group at year 2 compared with year 1, owing primarily to stability of the IOP-lowering effect in the Hydrus plus CS group and a decline in effect for the CS group. The observed difference in means was 2.3 mmHg at 24 months and was calculated from the DIOP of subjects who completed the 24-month washout. This difference is slightly lower than the 3 mmHg assumption used to calculate the sample size of the study because of the stronger IOP response in the CS group than expected. Imputation of previously observed washed out DIOP values for missing data increases this difference, because the number of patients who could not undergo washout was higher in the CS group than in the Hydrus plus CS group (10 vs. 3 patients), and the missing subjects tended toward higher IOP. The reported result, therefore, represents a conservative estimate of the difference in IOP favoring the CS group.

The observed decay in IOP-lowering effect in the CS arm from 12 to 24 months is consistent with the OHTS findings, where the decrease in effect was estimated at 0.05 mmHg per month of follow-up. The rate of degradation of the IOP-lowering effect in the CS group within HYDRUS II seems to be approximately twice the level observed in OHTS, which may be related to the higher baseline IOP and the greater initial effect. A 3-year follow-up is underway to assess long-term IOP change further.

The safety observations in this study are of particular importance given the mild to moderate disease severity in the study cohort. There was no difference in visual acuity between the 2 study groups from the early postoperative period through the 2-year follow-up; any loss of BCVA was rare in this study. More than 90% of subjects experienced stable to improved vision, which is expected after CS. Ocular

health adverse findings were typical for those seen in a CS population and were limited to the minor and transient effects of surgery. Typical safety risks for traditional incisional glaucoma surgery, such as hypotony, vision loss, infections, and bleb-related complications, were completely absent from the Hydrus plus CS group, as expected for a MIGS procedure.

Although this study used several design features to improve the standard of evidence for device effectiveness, several limitations remain. Masking the surgeon to the assigned treatment was not possible, and because the microstent is visible on the slit lamp with gonioscopic examination, masking the treatment group from the IOP assessor during follow-up visits also was not possible. Compliance with the follow-up washout regimen in a progressive disease such as glaucoma can be increasingly difficult over time. However, the study aimed to include patients who were not candidates for filtering surgery at the time of enrollment and who, in the judgment of the investigator, could undergo washout safely. Nonetheless, several patients did not wash out medications for safety reasons, especially in the second year of follow-up. This led to a higher number of non–washed-out patients in the CS group, which in the intention-to-treat analysis led to more failures in this group. The investigators considered the possible effect of the asymmetrical wash out rate on the study results. In a separate analysis, the difference in treatment response rate was evaluated only for the subjects who completed the 2-year washout. This type of analysis should improve the response rate in both groups, because the worst cases are omitted from the analysis. As expected, the response rate increased in both groups. In this scenario, 40 (88.9%) of 45 patients versus 23 (63.9%) of 36 patients met the end point. Despite the reduced number, a 2-sided Fisher exact test would have shown statistical significance ($P = 0.0140$). Therefore, the conclusion regarding the significance of the treatment effect remains unchanged. Another limitation is that studies involving a minimum qualifying IOP for study entry are inherently subject to regression to the mean, unless the average of multiple assessments are taken over several prequalifying visits. Having patients return for multiple baseline visits for IOP measurement may not be practical for study subjects and investigators, especially under washout conditions. Also, like any study involving an investigational device, this study was performed early in the investigator's surgical experience with the Hydrus device. Finally, the study was conducted in a white population at a small number of centers. A large-scale multicenter, controlled, randomized study designed to address many of these limitations is underway in the North America, Europe, and Asia.

Although several small or single-center case series for MIGS devices have been published, only 1 other study was a controlled, multicenter, randomized clinical trial (iStent Trabecular Bypass; Glaukos Corp, Laguna Hills, CA). The 1- and 2-year results were published separately.28, 29 Like HYDRUS II, this study compared a MIGS device plus CS with CS alone in glaucoma patients. Comparing the 2 trials, the iStent study was larger (240 eyes), it was conducted before the American National Standards Institute study recommendations described previously, and it did not incorporate follow-up medication washout, DIOP measurements, or masked tonometry. The populations were similar in terms of glaucoma diagnosis and cataract, although HYDRUS II patients had higher average baseline washout IOP, mean medication use per patient, and more advanced glaucoma based on visual field assessment. The 1 comparable outcome measure for the 2 studies was the proportion of unmedicated patients with a 20% or more reduction in IOP at 12 and 24 months. In the iStent study, there was no follow-up washout; thus, a subject was considered to have failed treatment if medications were in use at the follow-up period. Evaluating only the unmedicated subjects in the HYDRUS II study, the between-group difference (MIGS plus CS vs. CS alone) for subjects with a 20% or more reduction in IOP at 12 months was 23% in HYDRUS II versus 18% in the iStent study. The results differed substantially in the second year of follow-up, where the between-group difference in HYDRUS II was 39% versus 9% in the iStent study. This finding suggests a more durable treatment effect with the Hydrus device.

In conclusion, the HYDRUS II study demonstrated that implantation of the Hydrus Microstent in patients undergoing CS provided a significant reduction in IOP and medication use compared with

CS alone for 2 years after surgery. Cataract surgery alone also was found to reduce IOP and medication use compared with preoperative levels, although the effect was observed to decrease in the second year of follow-up. Follow-up visual acuity was unaffected by the presence of the device, and whereas focal PAS were observed more frequently in the Hydrus plus CS group, the rate of all other adverse events was similar. Thus, Hydrus Microstent implantation when performed with CS is an effective and safe procedure.

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References

1. Quigley HA, Broman AT. The number of people with glaucoma worldwide in 2010 and 2020. Br J Ophthalmol 2006;90:262–7.

2. American Academy of Ophthalmology. Preferred Practice Pattern: Primary Open-Angle Glaucoma. San Francisco, CA: American Academy of Ophthalmology; 2010.

3. Lichter PR, Musch DC, Gillespie BW, et al. Interim clinical outcomes in the Collaborative Initial Glaucoma Treatment Study comparing initial treatment randomized to medications or surgery. Ophthalmology 2001;108:1943–53.

4. Heijl A, Leske MC, Bengtsson B, et al. Reduction of intraocular pressure and glaucoma progression: results from the Early Manifest Glaucoma Trial. Arch Ophthalmol 2002;120:1268–79.

5. The Advanced Glaucoma Intervention Study (AGIS): 7. The relationship between control of intraocular pressure and visual field deterioration. The AGIS Investigators. Am J Ophthalmol 2000;130:429–40.

6. Baudouin C, Renard JP, Nordmann JP, et al. Prevalence and risk factors for ocular surface disease among patients treated over the long term for glaucoma or ocular hypertension. Eur J Ophthalmol 2013;23:47–54.

7. Tsai JC, McClure CA, Ramos SE, et al. Compliance barriers in glaucoma: a systematic classification. J Glaucoma 2003;12: 393–8.

8. Tsai JC. A comprehensive perspective on patient adherence to topical glaucoma therapy. Ophthalmology 2009;116:S30–6.

9. Tsai T, Robin AL, Smith JP 3rd. An evaluation of how glaucoma patients use topical medications: a pilot study. Trans Am Ophthalmol Soc 2007;105:29–33; discussion 35.

10. Broadway DC, Chang LP. Trabeculectomy, risk factors for failure and the preoperative state of the conjunctiva. J Glaucoma 2001;10:237–49.

11. Samples JR, Ahmed IK, eds. Surgical Innovations in Glaucoma. New York: Springer-Verlag; 2013.

12. Spiegel D, Kobuch K. Trabecular meshwork bypass tube shunt: initial case series. Br J Ophthalmol 2002;86:1228–31.

13. Hoeh H, Ahmed IK, Grisanti S, et al. Early postoperative safety and surgical outcomes after implantation of a suprachoroidal micro-stent for the treatment of open-angle glaucoma concomitant with cataract surgery. J Cataract Refract Surg 2013;39:431–7.

14. Lewis RA. Ab interno approach to the subconjunctival space using a collagen glaucoma stent. J Cataract Refract Surg 2014;40:1301–6.

15. Gedde SJ, Schiffman JC, Feuer WJ, et al. Treatment outcomes in the Tube Versus Trabeculectomy (TVT) study after five years of follow-up. Am J Ophthalmol 2012;153:789–803.

16. Johnstone M, Saheb H, Ahmed IK, et al. Effects of a Schlemm canal scaffold on collector channel ostia in human anterior segments. Exp Eye Res 2014;119:70–6.

17. American National Standards Institute. ANSI Z80. 27d2001 (R2014). Ophthalmics: Aqueous Shunts for Glaucoma Application. American National Standards Institute, Alexandria, VA; 2001.

18. Gordon MO, Kass MA. The Ocular Hypertension Treatment Study: design and baseline description of the participants. Arch Ophthalmol 1999;117:573–83.

19. Ko GY, Song HY, Seo TS, et al. Obstruction of the lacrimal system: treatment with a covered, retrievable, expandable nitinol stent versus a lacrimal polyurethane stent. Radiology 2003;227:270–6.

20. Verheye S, De Meyer G, Salu K, et al. Histopathologic evaluation of a novel-design nitinol stent: the Biflex stent. Int J Cardiovasc Interv 2004;6:13–9.

21. Beeley NRF, Stewart JM, Tano R, et al. Development, implantation, in vivo elution, and retrieval of a biocompatible, sustained release subretinal drug delivery system. J Biomed Mater Res 2006;76:690–8.

22. Olson JL, Velez-Montoya R, Erlanger M. Ocular biocompatibility of Nitinol intraocular clips. Invest Ophthalmol Vis Sci 2012;53:354–60.

23. Grierson I, Saheb H, Kahook M, et al. A novel Schlemm's canal scaffold: histologic observations. J Glaucoma. 2013 November 14. [ePub ahead of print].

24. Camras LJ, Yuan F, Fan S, et al. A novel Schlemm's Canal scaffold increases outflow facility in a human anterior segment perfusion model. Invest Ophthalmol Vis Sci 2012;53:6115–21.

25. Gulati V, Fan S, Hays CL, et al. A novel 8-mm Schlemm's canal scaffold reduces outflow resistance in a human anterior segment perfusion model. Invest Ophthalmol Vis Sci 2013;54: 1698–704.

26. Leske MC, Heijl A, Hussein M, et al. Factors for glaucoma progression and the effect of treatment: the Early Manifest Glaucoma Trial. Arch Ophthalmol 2003;121:48–56.

27. Fea A. Phacoemulsification versus phacoemulsification with microbypass stent implantation in primary open-angle glaucoma. J Cataract Refract Surg 2010;36:407–12.

28. Samuelson TW, Katz LJ, et al. Randomized evaluation of the trabecular micro-bypass stent with phacoemulsification in patients with glaucoma and cataract. Ophthalmology 2011;118: 459–67.

29. Craven ER, Katz LJ, et al. Cataract surgery with trabecular micro-bypass stent implantation in patients with mild-to-moderate open-angle glaucoma and cataract: two-year follow-up. J Cataract Refract Surg 2012;38: 1339–45.

30. Summary of safety and effectiveness for the Glaukos iStent. PMA P080030 2012;21e2.

31. Shingleton BJ, Gamell LS, O'Donoghue MW, et al. Long term changes in intraocular pressure after clear corneal phacoemulsification: normal patients versus glaucoma suspects and glaucoma patients. J Cataract Refract Surg 1999;25:885–90.

32. Hayashi K, Hayashi H, Nakao F, et al. Effect of cataract surgery on intraocular pressure control in glaucoma patients. J Cataract Refract Surg 2001;27:1779–86.

33. Poley BJ, Lindstrom RL, Samuelson TW. Long-term effects of phacoemulsification with intraocular lens implantation in Ophthalmology Volume 122, Number 7, July 2015 1292 normotensive and ocular hypertensive eyes. J Cataract Refract Surg 2008;34:735–42.

34. Mansberger SL, Gordon MO, Jampel H, et al. Reduction in intraocular pressure after cataract extraction: the Ocular Hypertension Treatment Study. Ophthalmology 2012;119:1826–31.

35. Poley BJ, Lindstrom RL, Samuelson TW, et al. Intraocular pressure reduction after phacoemulsification with intraocular lens implantation in glaucomatous and nonglaucomatous eyes: evaluation of a causal relationship between the natural lens and open-angle glaucoma. J Cataract Refract Surg 2009;35:1946–55.

36. Barnett AG, Van der Pols JC, Dobson A. Regression to the mean: what it is and how to deal with it. Int J Epidemiol 2005;34:215–20.

Figures

Figure 1. The Hydrus Microstent (Ivantis, Inc, Irvine, CA) is 8 mm in length. The 7-mm scaffold segment resides within the lumen of Schlemm's canal, and the 1-mm inlet portion resides within the anterior chamber. The microstent is designed to fit the curvature of the canal without obstructing collector channel ostia located along the posterior wall.

(Photograph courtesy Jason Jones, MD.)

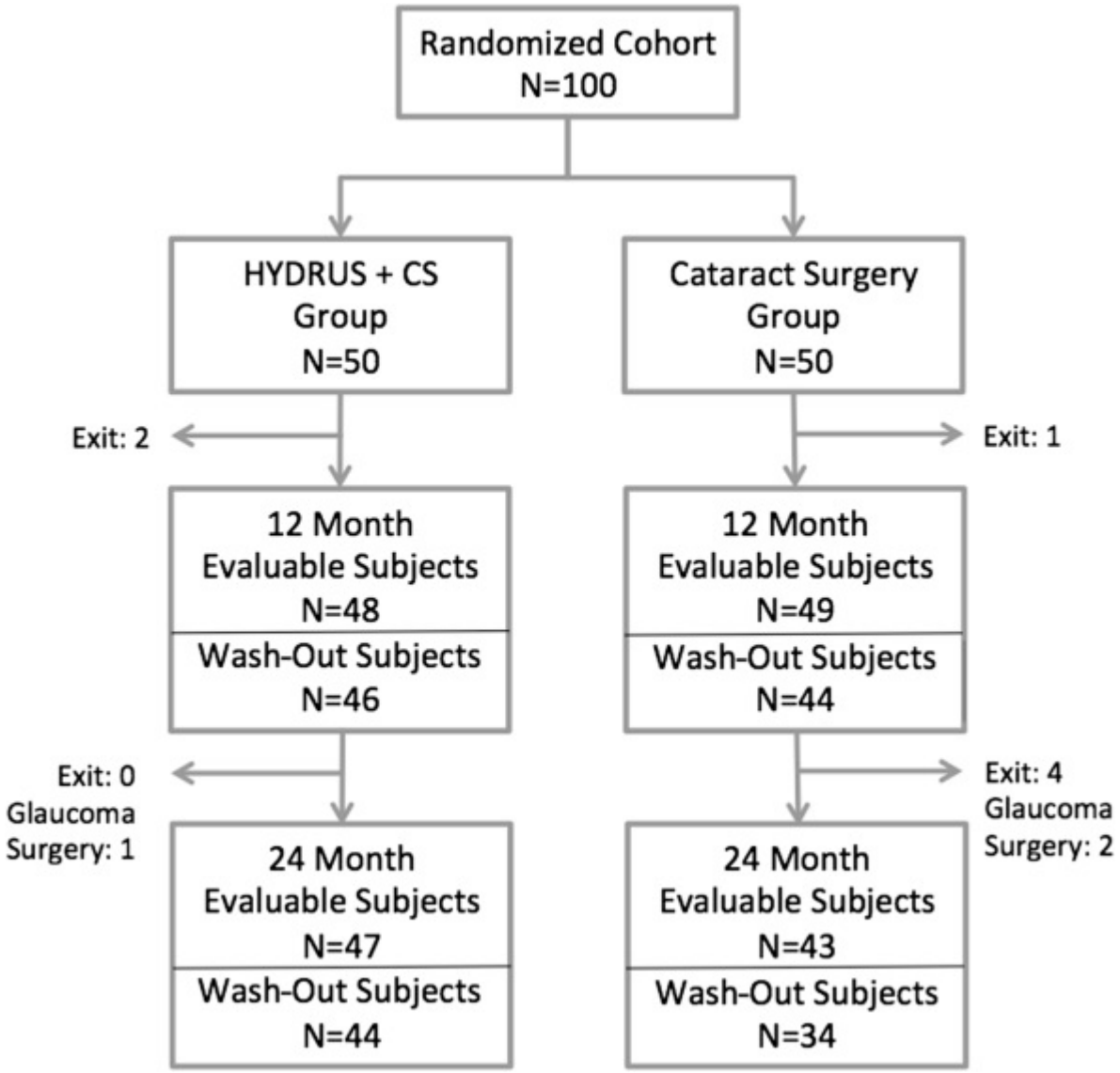

Figure 2. Flowchart showing patient disposition from randomization through 2 years of follow-up. CS = cataract surgery.

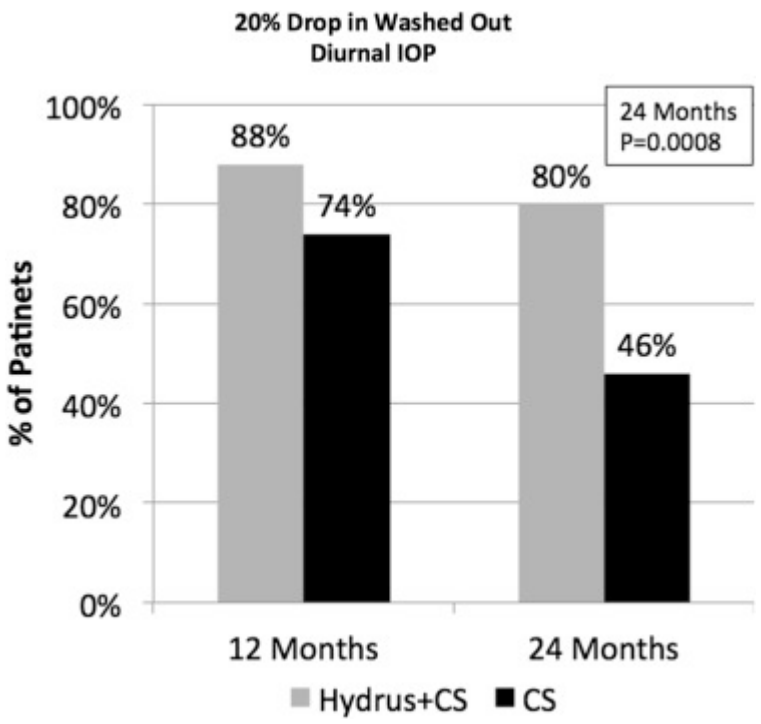

Figure 3. Bar graph showing that a significantly higher proportion of patients receiving the microstent obtained a 20% or more drop in washed out diurnal intraocular pressure (IOP) over the course of the study compared with controls. The 12-month difference was not significant (P = 0.1247). n = 50 per group. CS = cataract surgery.

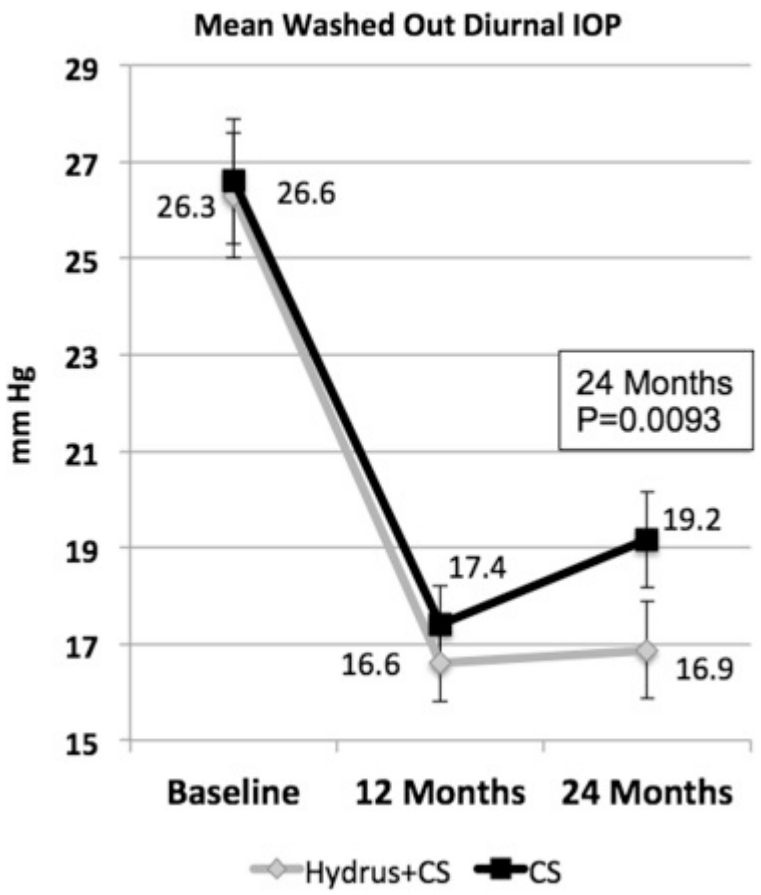

Figure 4. Graph showing the washed out mean diurnal intraocular pressure (IOP) from baseline through 2 years of follow-up. The 24-month mean diurnal IOP was significantly lower in the Hydrus plus cataract surgery (CS) group. The error bars represent the 95% confidence interval for the mean. Baseline: n = 50 each group; 12 months: n = 46 for the Hydrus plus CS group and n = 44 for the CS group; 24 months: n = 44 for the Hydrus plus CS group and 34 for the CS group.

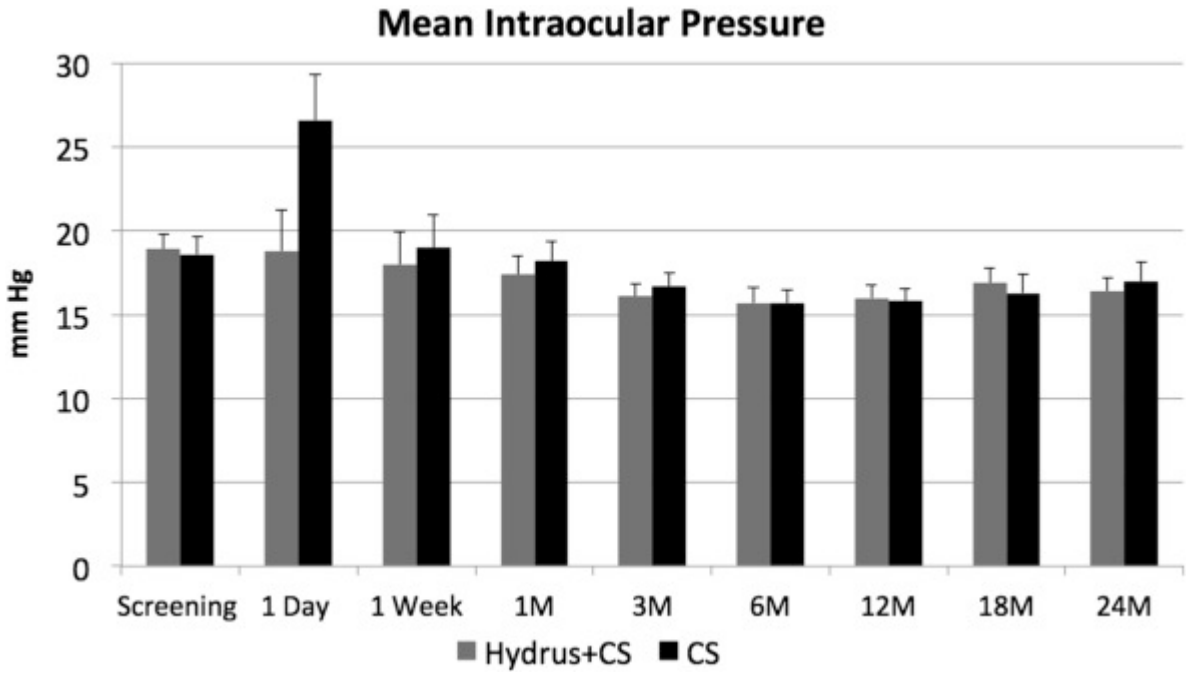

Figure 5. Graph showing the mean medicated intraocular pressure (IOP) at each study visit. Error bars denote 95% confidence intervals for the mean. CS = cataract surgery; M = month(s).

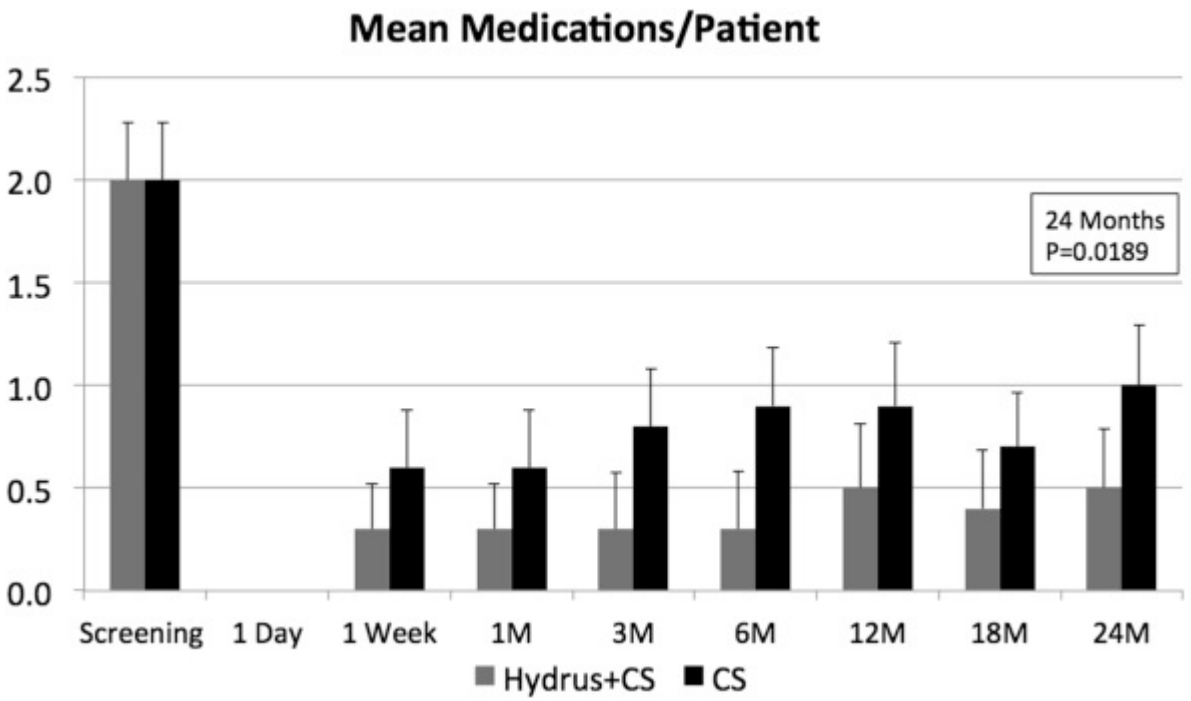

Figure 6. Bar graph showing the mean number of medications per patient at each study visit. Error bars denote 95% confidence intervals for the mean. CS = cataract surgery; M = month(s).

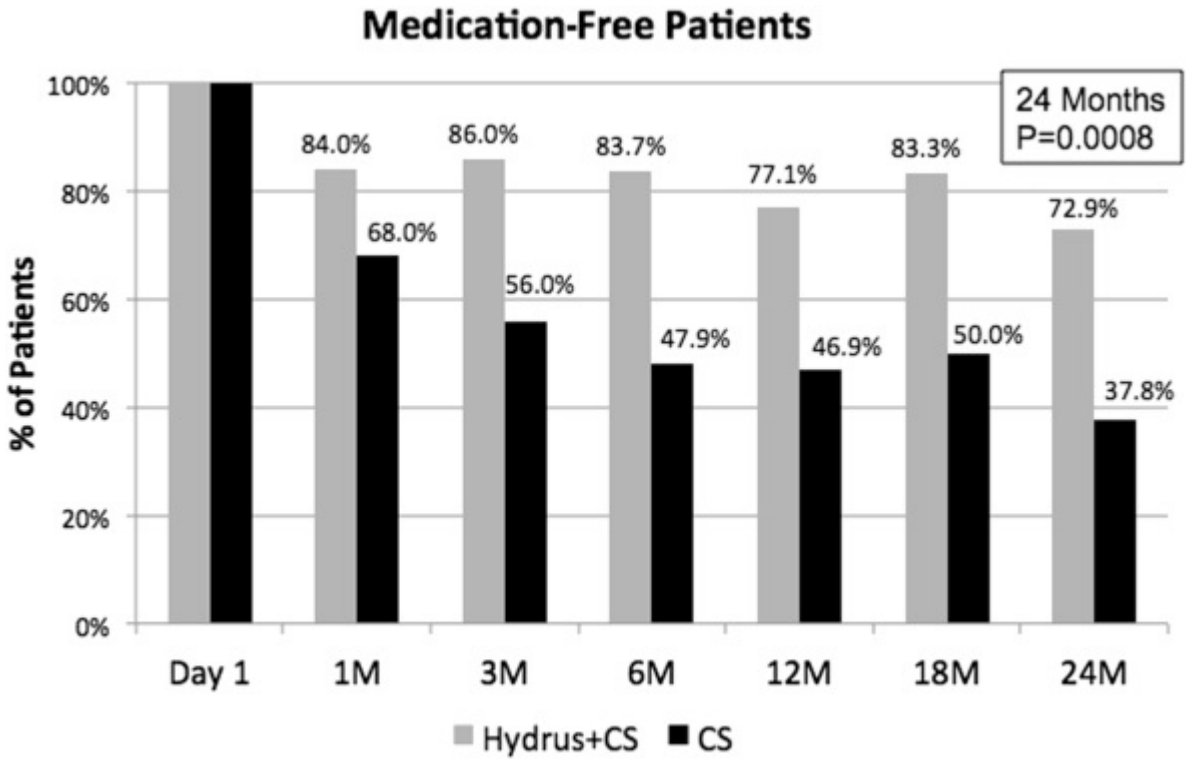

Figure 7. Bar graph showing the proportion of patients maintained at controlled intraocular pressure without the use of ocular hypotension medications throughout the follow-up period. At 24 months, there was a 45.1% difference between groups. The 12 and 24 month (M) values represent medication-free percentages before washout. CS = cataract surgery.

Tables

Table 1. Baseline Characteristics of the Study Population

Characteristic	**Hydrus and Cataract Surgery Group (n = 50)**	**Cataract Surgery Group (n = 50)**	***P* Value**
Mean age ± SD, yrs	72.8±6.6	71.5±6.9	0.3498
Male, no. (%)	20 (40.0)	29 (58.0)	0.1091
Race, no. (%)			
White	48 (96.0)	49 (98.0)	1.0000
Hispanic	1 (2.0)	0 (0.0)	1.0000
Asian	1 (2.0)	0 (0.0)	1.0000
Study eye, no. (%)			
Right	27 (54.0)	27 (54.0)	1.0000
Left	23 (46.0)	23 (46.0)	1.0000
Baseline BCVA (range), ETDRS	20/44 (20/13–20/160)	20/40 (20/16–20/400)	0.3784
Mean pachymetry ± SD, µm	539±32	532±29	0.2756
Glaucoma diagnosis, no. (%)			
POAG	45 (90.0)	41 (82.0)	0.3881
Pseudoexfoliative glaucoma	5 (10.0)	8 (16.0)	0.5536
Pigmentary glaucoma	0 (0.0)	1 (2.0)	1.0000
Previous trabeculoplasty	0 (0.0)	1 (2.0)	1.0000
Mean visual field ± SD			
MD	−5.6±5.4	−8.4±7.8	0.0449
PSD	5.1±4.6	5.2±4.3	0.9589
Mean medicated IOP at screening±SD, mmHg	18.9±3.3	18.6±3.8	0.6517
Mean no. of hypotensive medications ± SD	2.0±1.0	2.0±1.1	0.7610
Patients taking medications, no. (%)			
0	1 (2.0)	1 (2.0)	1.0000
1	18 (36.0)	16 (32.0)	0.8330
2	17 (34.0)	18 (36.0)	1.0000
3	10 (20.0)	11 (22.0)	1.0000
4	4 (8.0)	4 (8.0)	1.0000
Type of medications, no. (%)			
Prostaglandin analog	40 (80)	38 (76)	0.8097

Characteristic	Hydrus and Cataract Surgery Group (n = 50)	Cataract Surgery Group (n = 50)	*P* Value
β-blocker	32 (64)	28 (56)	0.5406
Carbonic anhydrase inhibitor	14 (28)	26 (52)	0.0242
α-adrenergic agonist	11 (22)	6 (12)	0.2869
β-adrenergic antagonist	0 (0)	0 (0)	—
Mean washed-out DIOP±SD, mmHg	26.3±4.4	26.6±4.2	0.7147

BCVA = best-corrected visual acuity; DIOP = diurnal intraocular pressure; ETDRS = Early Treatment Diabetic Retinopathy Study; IOP = intraocular pressure; MD = mean deviation; POAG = primary open-angle glaucoma; PSD = pattern standard deviation; SD = standard deviation.

Table 2. Adverse Events

	Year 1			Year 2		
	HYDRUS + Cataract Surgery (n = 50)	Cataract Surgery (n = 50)	*P* Value	HYDRUS + Cataract Surgery (n = 48)	Cataract Surgery (n = 49)	*P* Value
Ocular adverse events in the study eye						
Retinal detachment	0 (0.0)	1 (2.0)	1.0000	0 (0.0)	0 (0.0)	—
Postoperative wound dehiscence	0 (0.0)	1 (2.0)	1.0000	0 (0.0)	0 (0.0)	—
Anterior ischemic optic neuropathy	0 (0.0)	1 (2.0)	1.0000	0 (0.0)	0 (0.0)	—
BCVA loss >2 lines	0 (0.0)	3 (6.0)	0.2424	0 (0.0)	1 (2.0)	1.0000

	Year 1			Year 2		
	HYDRUS + Cataract Surgery (n = 50)	**Cataract Surgery (n = 50)**	***P* Value**	**HYDRUS + Cataract Surgery (n = 48)**	**Cataract Surgery (n = 49)**	***P* Value**
IOP spike (>10 mmHg more than baseline)	2 (4.0)	2 (4.0)	1.0000	0 (0.0)	0 (0.0)	—
Macular edema	1 (2.0)	2 (4.0)	1.0000	0 (0.0)	0 (0.0)	—
Retinal detachment	0 (0.0)	1 (2.0)	1.0000	0 (0.0)	0 (0.0)	—
Vitreal macular traction	0 (0.0)	1 (2.0)	1.0000	1 (2.1)	0 (0.0)	0.4948
Epiretinal membrane	0 (0.0)	2 (4.0)	0.4949	0 (0.0)	1 (2.0)	1.0000
Focal PAS	6 (12.0)	1 (2.0)	0.1117	9 (18.8)	1 (2.0)	0.0077
Optic disc hemorrhage	1 (2.0)	0 (0.0)	1.0000	0 (0.0)	0 (0.0)	—
Repeat surgical intervention						
Secondary glaucoma surgery	0 (0.0)	0 (0.0)	—	1 (2.1)	2 (4.1)	1.0000

BCVA = best-corrected visual acuity; IOP = intraocular pressure; PAS = peripheral anterior synechiae.

Data are no. (%) unless otherwise indicated. *P* values are reported for non-zero frequency observations.