Endoscopic Cyclophotocoagulation (ECP) in the Management of Uncontrolled Glaucoma With Prior Aqueous Tube Shunt

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Purpose: To evaluate the efficacy and safety of endoscopic cyclophotocoagulation (ECP) in the treatment of uncontrolled glaucoma with a prior aqueous tube shunt.

Methods: A prospective, nonrandomized, interventional clinical trial with up to 2 years of follow up included 25 eyes of 25 consecutive glaucoma patients with a previous tube shunt and uncontrolled intraocular pressure (IOP) despite medical therapy. Patients had IOP greater than 21 mm Hg on maximal medications or IOP $\leq$21 mm Hg but intolerant to medications or using an oral carbonic anhydrase inhibitor. Application of ECP over 360 degrees was performed and subjects were followed for 6 months minimum. Main outcome measures were mean reduction in IOP and medications at 12 months. Success was defined as reduction in IOP of 3 mm Hg and discontinuation of nontolerated glaucoma medications. A failure was defined as continued uncontrolled IOP, vision loss to no light perception, or additional medications or glaucoma surgery required.

Results: At 12 months, the mean IOP dropped from 24.02 to 15.36 mm Hg. The mean of the differences was -7.77 mm Hg (-30.8%). The mean number of medications was 3.2 before laser and 1.5 at 12 months ($P<0.001$). The success rate at 12 months ($n=18$) was 88% and remained at that level until the end of the follow-up period of 2 years ($n=11$, $P<0.00005$). There were no serious complications.

Conclusions: ECP seems to be a safe and effective treatment in patients with uncontrolled IOP with a prior aqueous tube shunt, and is a reasonable option in this group of refractory glaucoma patients.

Key Words: glaucoma, aqueous tube shunt, endoscopic cyclophotocoagulation, ECP

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Aqueous tube shunt surgery is an increasingly common modality to treat glaucoma that is unresponsive to medical treatment, laser, or other filtering procedures. If a tube shunt remains open and functional but the intraocular pressure (IOP) rises above target levels, medical therapy is generally reinitiated. However, if maximal tolerated medical therapy fails to control IOP, there is no consensus of opinion as to the next step in treatment. Some advocate a second tube shunt, but there are risks of strabismus and tube or plate exposure and discomfort.[1] Others prefer a cyclodestructive procedure, but traditional methods such as cyclocryotherapy and transscleral cyclophotocoagulation risk complications of inflammation, hypotony, and phthisis.[2–7]

The target tissue of cyclodestructive procedures is the ciliary epithelium of the ciliary body, and the amount of energy delivered is determined by melanin absorption in the pigmented ciliary epithelium. Melanin energy absorption is maximal at wavelengths of 810 to 840 nm, with higher wavelengths transmitting more energy through the pigmented ciliary epithelium and into surrounding tissues.[8] Laser energy applied by an external approach would be more likely to cause collateral damage to the sclera and ciliary body stroma than that applied directly from an intraocular approach.

Hypothetically, the least destructive and most effective treatment is one that employs a laser with a wavelength of 810 to 840 nm, applied under direct observation and titratable to achieve the desired tissue effect. Uram developed such an instrument that combines a diode endolaser, aiming beam, light source, and endoscope in one intraocular probe to perform endoscopic cyclophotocoagulation (ECP), a controlled ciliary process treatment under direct visualization.[9–11] This device is designed to deliver the minimum necessary amount of energy to achieve the desired result.

We report our experience with ECP as a treatment modality to control IOP after prior placement of an aqueous tube shunt. In this prospective study, 25 eyes of 25 patients with a functional tube shunt and IOP uncontrolled with the addition of medications underwent ECP and were followed for a period of 6 months to 2 years. The primary outcome measures were reduction of IOP and number of medications at 12 months.

METHODS

Participants were recruited from consecutive patient visits to the clinical practice of an academic, tertiary referral center at the Doheny Eye Institute, with informed consent given before surgery. Approval from the Institutional Review Board of University of Southern California for research on human participants was obtained and all research conformed to the Declaration of Helsinki. Inclusion criteria were a diagnosis of open angle or angle closure glaucoma, greater than 6 months after previous glaucoma aqueous tube shunt surgery; IOP inadequately controlled (>21 mm Hg)

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on 2 or more topical glaucoma medications or with IOP ≤21 mm Hg but intolerant of medical therapy or on an oral carbonic anhydrase inhibitor, and visual acuity better than light perception. Exclusion criteria were neovascular glaucoma; visual acuity light perception or worse, prior transscleral ciliary body ablation (cyclophotocoagulation) procedures, or prior ECP; and nonfunctional (nonpatent) aqueous shunt without fluid drainage to plate. The patency of the tube shunt was assessed clinically by slit lamp biomicroscopy or by B scan ultrasound to determine the presence of a fluid bleb over the plate.

IOP was measured by Goldmann applanation tonometry by a trained certified ophthalmic technician. For the baseline IOP, the measurements taken on the 2 consecutive visits before surgery were averaged and the result used. Postoperative measurements were taken at the same time interval as baseline IOP within a 3 hours time period (8 to 11am, 11am to 2pm, and 2pm to 5pm). This was carried out in an attempt to minimize diurnal IOP fluctuation. The individual performing the measurement was not masked to the patient's surgical history, but also was not involved in the study.

The main outcome measure was mean reduction in IOP at 12 months after ECP, with a comparison of means of paired data points (paired t test,$\alpha = 0.05$), preoperatively and postoperatively. The proportion of successful treatment was calculated by a Kaplan-Meier survival curve analysis. Follow up was at 1, 3, 6, 12, 18, and 24 months.

Success was defined as a reduction in IOP of ≥ 3 mm Hg or a reduction in medications in the medication intolerant group, with IOP ≤21 mm Hg. A failure was defined as continued uncontrolled IOP (>21 mm Hg), vision loss to no light perception, and those requiring additional glaucoma medications or surgery.

Intervention

One surgeon (B.A.F.) performed all of the ECP surgical procedures under monitored anesthesia care with intravenous sedation and retrobulbar anesthesia with approximately 3 mL of lidocaine 1% and marcaine 0.5%. Dilation of the pupil was performed with cyclopentolate 1%, phenylephrine 2.5%, and mydriacil 2%. A 2.8 mm keratome blade was used to make 2 clear corneal incisions (temporally and nasally), and viscoelastic was injected into the anterior chamber and ciliary sulcus. The probe was inserted into the anterior chamber and advanced toward the ciliary sulcus. At that point, the monitor was used for endoscopic viewing of the ciliary processes. With the laser settings at 250 to 350 mW and continuous surgeon controlled duration, each ciliary process visible for 360 degrees was photocoagulated as well as the intervening spaces in between processes. The treatment endpoint was shrinkage and whitening of the entire ciliary process. The viscoelastic was removed from the eye with automated or manual (Simcoe) irrigation and aspiration. The corneal incisions were closed with 10-0 nylon or vicryl. A subconjunctival injection of 0.1 mL dexamethasone 1% and topical administration of tobramycin-dexamethasone ointment were performed at the conclusion of the procedure. Patients were instructed to continue their current glaucoma drop treatment regimen.

Patients were followed at 1 day, 1 week, and 1, 3, 6, 12, 18, and 24 months. Measurements included visual acuity, IOP, and any complications. After discharge from the surgical center, patients were placed on a topical antibiotic four times daily, prednisolone acetate 1% every 1 to 2 hours while awake, and flurbiprofen 2% three times daily. Antibiotic drops were discontinued after 7 to 10 days, and the steroids, nonsteroidal anti-inflammatory drugs, and glaucoma medications tapered as intraocular inflammation and pressure allowed.

Statistical Analysis

A power and sample size calculation was made before the start of the study, with a goal to detect a 15% IOP reduction with a significance level of 0.05 and 80% power. A paired t test was performed comparing preoperative IOP and IOP at 1, 3, 6, 12, 18, and 24 months; and mean number of medications taken preoperatively and postoperatively. The success rate is demonstrated as a Kaplan-Meier survival curve with cumulative success (failure is the defining point) plotted as a function of time from 1 to 24 months at 3 month intervals. Patients who failed were still included in the comparison of means, but censored from the survival curve from that point on.

RESULTS

Twenty-five eyes of 25 patients were enrolled in this study: 14 men (56%) and 11 women (44%) (Table 1). The mean age was 59 ± 17 years. Twelve patients (48%) had primary open angle glaucoma, 9 patients (36%) had secondary glaucoma (5 owing to corneal transplant, 2 to iridocorneal endothelial syndrome, and 2 to trauma), 3 patients (12%) had chronic angle closure glaucoma, and 1 patient (4%) with juvenile open angle glaucoma. A Baerveldt 350 implant (AMO, Santa Ana, CA) was present in 20 eyes, an Ahmed Glaucoma Valve (New World Medical, Rancho Cucamonga, CA) in 3 eyes, and 2 eyes had 2 aqueous shunts (a Baerveldt and Ahmed in 1, and 2 Baerveldts in the other).

The mean IOP preoperatively was 24.0 mm Hg (Table 2). Mean postoperative IOP at 6, 12, and 24 months was 14.9 (−8.7 or 32.4%), 15.4 (−7.8 or 30.8%), and 18.1 (−7.0 or 25.5%), respectively (all $P < 0.05$).

The mean number of medications prelaser was 3.2 (Table 3). The mean number of medications at 6, 12, and 24 months was 1.5 (−1.7 or 50%, $P < 0.001$), 1.5 (−1.6 or 49%, $P < 0.001$), and 2.0 (−1.5 or 37%, $P < 0.05$), respectively.

Cumulative success is shown by the Kaplan-Meier plot in Figure 1 and shows a success rate of 88% at 6, 12, and 24 months. Table 4 includes the number of participants at each time point with decreases owing to censoring for loss of follow up or earlier failure.

TABLE 1. Types of Glaucoma in Study Patients

Type of Glaucoma	N (%)	Male	Female
POAG	12 (48)	7	5
Secondary	9 (36)	5	4
PK	5 (20)		
ICE	2 (8)		
Traumatic	2 (8)		
CACG	3 (12)	1	2
JOAG	1 (4)	1	0
Total	25	14	11

CACG indicates chronic angle closure glaucoma; ICE, iridocorneal endothelial syndrome; JOAG, juvenile open angle glaucoma; PK, penetrating keratoplasty; POAG, primary open angle glaucoma.

TABLE 2. IOP Pre-ECP and Post-ECP in Patients With Open Angle or Angle Closure Glaucoma With Prior Aqueous Tube Shunt

Variable	N	Mean (SD)	Range	Mean Decrease From Prelaser IOP (%)	Confidence Interval (*P*)
IOP pre-ECP	25	24.02 (6.24)	15-44	—	—
IOP at 1 mo	25	12.93 (5.41)	2.5-26	11.09 (43.2%)	7.62, 14.56 $P<0.0001$
IOP at 3 mo	25	13.03 (3.36)	7.75-20	10.99 (42.0%)	7.79, 14.20 $P<0.0001$
IOP at 6 mo	23	14.93 (4.86)	8-25	8.75 (32.4%)	5.02, 12.47 $P<0.0001$
IOP at 12 mo	19	15.36 (3.80)	8-20.5	7.77 (30.8%)	4.65, 10.89 $P<0.0001$
IOP at 18 mo	14	18.11 (9.94)	11.3-51	6.50 (25.6%)	0.62, 12.38 $P=0.03$
IOP at 24 mo	11	18.08 (7.41)	8.5-32	6.96 (25.5%)	1.04, 12.89 $P=0.03$

ECP indicates endoscopic cyclophotocoagulation; IOP, intraocular pressure.

Complications seen were decrease in vision, corneal graft failure, and cystoid macular edema (CME). Analysis of visual acuity showed that 4 patients had a decrease in Snellen visual acuity of greater than 2 lines of vision, and 1 had an increase of visual acuity (Fig. 2). Of those with a decrease in vision, 1 was due to corneal edema, 2 to graft failure, and 1 to CME. Of the 5 patients with corneal transplant and glaucoma, 2 had graft failure. The corneal edema and CME resolved with treatment of topical steroids and nonsteroidal anti-inflammatory drops and vision returned to baseline. There were no cases of hypotony or phthisis, infection, visual loss to light perception, or strabismus.

DISCUSSION

With the early results of the tube versus trabeculectomy study, there may be a shift toward earlier implantation of aqueous tube shunts in refractory glaucoma or patients with prior intraocular surgery.[12] However, over the course of time, although a tube shunt remains patent, it may fail to adequately control IOP, even with the addition of glaucoma medications. This is thought to be due to increasing fibrosis of the capsule surrounding the plate which makes it less permeable to aqueous outflow.[13,14] Once this stage is reached, there is no consensus opinion as to the next step in treatment. An additional tube shunt has an increased risk of strabismus, tube shunt exposure, and discomfort. Transscleral cyclodestructive procedures have risks of hypotony, phthisis, vision loss, and inflammation. ECP has exhibited a significantly lower incidence of these complications, and in this study we examine its use in the treatment of glaucoma with persistent elevated IOP in the presence of a prior patent aqueous tube shunt.

ECP has previously been evaluated retrospectively by Chen et al[15] in the treatment of refractory glaucoma, including primary open angle glaucoma, congenital, chronic angle closure, uveitic, pseudoexfoliation, neovascular, and angle recession. Using a success definition of IOP $\leq$21 mm Hg with or without medications, they found a success rate of 94% at 1 year and 82% after 2 years of follow up. Mean glaucoma medications decreased from a mean of 3.0 ± 1.3 to 2.0 ± 1.3 at last follow-up. Complications included fibrin (24%), hyphema (12%), CME (10%), and choroidal effusion (4%).

Another trial prospectively compared ECP to the Ahmed Valve with alternating allocation in 68 patients with uncontrolled IOP ($\geq$35 mm Hg) on medications with a definition of success of IOP between 6 and 21 mm Hg with or without medications.[16] ECP was performed via a pars plana approach with approximately 210 degrees of treatment of the ciliary processes extending into the pars plana. The success rate at 2 years was similar in both the groups; 71% for the Ahmed group and 74% with ECP.

A randomized prospective trial comparing cataract extraction combined with trabeculectomy versus ECP was performed by Gayton and coauthors.[17] In this trial, 58 patients with glaucoma and either IOP $\geq$30 mm Hg, or progressive cupping or visual field loss were treated with cataract surgery combined with trabeculectomy (only 14 patients with antimetabolites) or ECP 240 to 270 degrees. Success was defined as IOP $<$19 mm Hg with a stable visual field and optic nerve. They found a similar decrease in IOP (trabeculectomy = 32%, ECP = 29%), and success rate (trabeculectomy = 72%, ECP = 77%) at 6 months. The success of trabeculectomy without medications was higher than ECP (54% vs. 32%).

To our knowledge, ours is the first study of ECP in the treatment of glaucoma with prior aqueous tube shunt. We prospectively followed patients for up to 2 years, with the

TABLE 3. Glaucoma Medications Pre-ECP and Post-ECP

Time	N	Mean No. Medications (SD)	Mean Decrease From Prelaser No. Medications (%)	Confidence Interval (*P*)
Prelaser	25	3.2 (0.99)		
1 mo	25	2 (1.26)	1.16 (35.8)	0.57, 1.75 $P=0.0005$
3 mo	25	1.8 (1.38)	1.36 (42.7)	0.82, 1.90 $P<0.0001$
6 mo	23	1.47 (1.24)	1.65 (50)	1.03, 2.72 $P<0.0004$
12 mo	19	1.47 (1.31)	1.63 (49.1)	0.91, 2.35 $P=0.0002$
18 mo	14	1.64 (1.45)	1.64 (44.6)	0.64, 2.65 $P=0.004$
24 mo	11	2 (1.61)	1.45 (37.1)	0.20, 2.71 $P=0.03$

ECP indicates endoscopic cyclophotocoagulation.

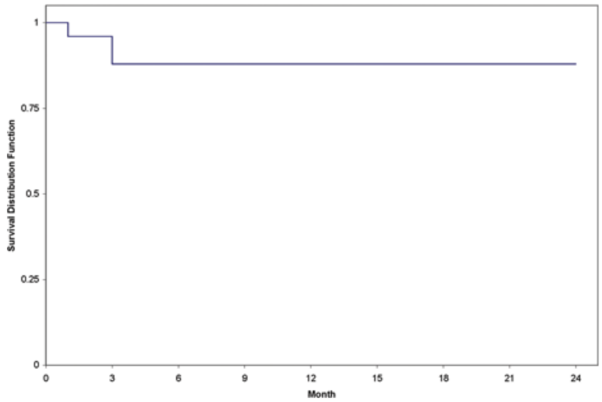

FIGURE 1. Kaplan-Meier survival curve showing cumulative success after endoscopic cyclophotocoagulation after aqueous tube shunt in glaucoma.

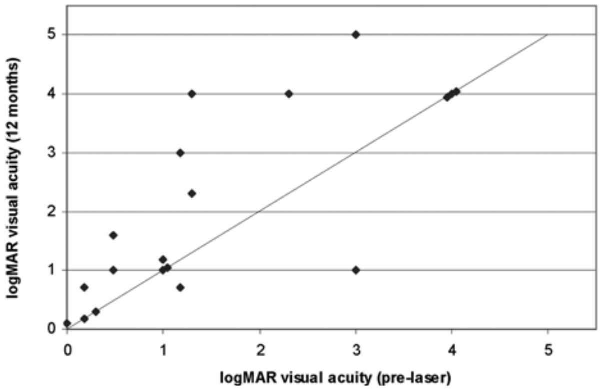

FIGURE 2. Scatter plot comparing the visual acuity before endoscopic cyclophotocoagulation with preexisting glaucoma aqueous tube shunt versus 12 months after procedure. logMAR indicates logarithm of the minimum angle of resolution.

primary endpoints of IOP and glaucoma medications compared with baseline. At 6 to 24 months, there was a 23% to 35% decrease in IOP, with an accompanying decrease in glaucoma medications of 1.5 to 1.8 per person. The cumulative success rate was 88% at 6 months and remained at this level at last follow up of 2 years. All recorded failures were due to lack of response in control of IOP, resulting in 1 patient requiring additional medications and 2 others requiring the continued use of oral carbonic anhydrase inhibitors.

The main outcome measures of IOP and glaucoma medications were set at 12 months in our study. The reduction of both measures remains stable through this time, but there is a gradual upward trend in both IOP and glaucoma medications between 1 and 2 years (Tables 2 and 3). The success rate remains the same, however, as the upward trend is below the threshold definition for failure. In addition, the number of subjects retained at these later time points is smaller. Nevertheless, as with other glaucoma surgeries, one may expect to see a gradual upward trend of IOP, medication use, and increased failure rate as time passes.

Of note is the retention of follow up which was excellent at 6 months (21 of 25 or 84%), but dropped to 18 of 25 (72%) at 12 months. Data was available for 11 of 25 (44%) at 2 years in part owing to loss of follow up, but also owing to some patients not yet reaching this time point. The retention rate of this study at 1 year (our primary endpoint) is high enough to make these results meaningful. Also, our ECP treatment may be more aggressive than prior studies, as we performed as near as possible to a 360 degrees treatment in all patients. Finally, the incidence of corneal graft rejection in our series bears further study. Because these eyes had already undergone multiple surgeries, including aqueous tube shunts, there is no way to know if ECP is a significant risk factor for corneal transplant failure. To better answer this question, we plan to compare cornea transplant patients undergoing aqueous shunt versus ECP as a primary glaucoma procedure.

Hypothetically, the addition of an aqueous inflow procedure to an existing outflow procedure should exhibit good success in the reduction of IOP and glaucoma medications. Indeed, our study supports the efficacy and safety of ECP in the treatment of uncontrolled glaucoma with a prior aqueous tube shunt. This surgical treatment of the ciliary processes should be considered as an alternative to an additional tube shunt or transscleral cycloablation in this group of patients.

TABLE 4. Survival Function of Success After Endoscopic Cyclophotocoagulation After Aqueous Tube Shunt Surgery

Follow Up (mo)	No. at Risk	No. of Failures	Cumulative Success (SE)
1	25	1	0.96 (0.04)
3	24	2	0.88 (0.07)
6	18	0	0.88 (0.07)
12	15	0	0.88 (0.07)
18	9	0	0.88 (0.07)
24	7	0	0.88 (0.07)

Success is defined as reduction in IOP of 3 mm Hg or greater, or discontinuation of nontolerated medication while maintaining IOP control. The number at risk represents the total starting number minus those censored at the previous time interval (dropout and failure).

IOP indicates intraocular pressure.

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