

Patient Outcomes Following Micropulse Transscleral Cyclophotocoagulation: Intermediate-term Results

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Purpose: To report the safety and efficacy outcomes following micropulse transscleral cyclophotocoagulation (MPTSCPC) procedure in patients with uncontrolled glaucoma.

Materials and Methods: Longitudinal retrospective cohort, multicenter study. Patients with different types of glaucoma who underwent MPTSCPC with P3 probe between July 2015 and May 2017. Patients were treated by different glaucoma specialists from 5 different locations (Tulane Study Group). Data on preoperative characteristics, surgical procedure(s) performed, and postoperative outcomes were collected and analyzed. Statistical analysis using logistic regression and Kaplan-Meier analysis was performed with Stata software. Intraoperative and postoperative complications, intraocular pressure, visual acuity, need for incisional glaucoma surgery, need for repeat micropulse, and number of topical medications were studied.

Results: One hundred ninety-seven eyes from 161 patients were included. Median follow-up was 12 months [interquartile range (IQR), 6 to 14]. Glaucoma diagnosis included 141 primary open-angle glaucoma (POAG), 8 neovascular glaucoma, and 12 others. The total success rate was 71%. Two percent (4 patients) developed postoperative cystoid macular edema. Preoperative mean intraocular pressure (SD) was 22 ± 9 and 16 ± 6 mm Hg at last follow-up ($P < 0.001$). Median preoperative logMAR visual acuity (IQR) was 0.4 (0.2 to 1.0) and 0.3 (0.2 to 1.0) at last follow-up ($P = 0.65$, Wilcoxon signed-rank test). Median number (IQR) of topical medications was 3 (1 to 4) preoperative and 2 (1 to 3) at last follow-up ($P < 0.001$). Kaplan-Meier analysis indicated 90% of patients free from repeat MPTSCPC at 12 months. Multivariable logistic regression identified 3 significant independent predictors of total success: diagnosis ($P = 0.011$) (POAG), previous glaucoma surgery ($P = 0.003$), and other concurrent procedures ($P = 0.013$).

Conclusions: Our large longitudinal cohort study has provided evidence that MPTSCPC is a safe and generally effective option in the treatment of POAG up to 12 months.

Key Words: glaucoma treatment, laser diode, micropulse

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Glaucoma is one of the leading causes of irreversible blindness worldwide.¹ Glaucoma therapies are designed either to increase the outflow or decrease the inflow of aqueous humor in order to decrease intraocular pressure (IOP) and preserve residual optic nerve function. Cyclophotocoagulation (CPC) is a form of glaucoma treatment using a laser with infrared wavelength of 810 nm to target the melanin in the pigmented ciliary body epithelium and thereby destruct the ciliary body; this results in decreased aqueous production and hence IOP.^{2–6} Traditional transscleral cyclophotocoagulation using continuous wave diode has been reserved for refractory glaucoma cases with poor visual potential due to the risk of phthisis, hypotony, visual deterioration, and unpredictability.^{3,7–10} The increased risk is thought to be largely from the nonselective nature of the traditional continuous wave diode laser.^{3,10}

A new method of TCP has been described that uses a micropulse diode laser [micropulse transscleral cyclophotocoagulation (MPTSCPC)] and trans pars plana treatment with a contact probe, which is thought to be more safe and at least equally effective as traditional diode laser due to more selective targeting of tissues.¹¹ The micropulse laser has been previously used for retinal procedures and now starting to be used in CPC.^{12–17} This method of laser delivery is advantageous because it delivers a series of repetitive and brief pulses of laser energy separated by rest periods, in contrast to traditional continuous wave lasers that deliver continuous intense energy to the ciliary body.^{12–19} This method of laser delivery is also thought to produce more selective targeting of ciliary body epithelium and less collateral damage.^{12–19} These “on” and “off” cycles allow energy to build up in the target tissue during the on cycle and allow the adjacent nonpigmented structures to cool off during the off cycles. The lower energy of the micropulse laser is also thought to augment uveoscleral outflow, in addition to decreasing the aqueous production.²⁰ Previous histologic studies have indicated no changes in the visually significant change in the tissues after micropulse laser through ultrasound biomicroscopy.²¹ The finer control of photothermal effects using MPTSCPC will hopefully allow cycloablation to be used as an earlier therapeutic option for eyes with good visual potential, rather than for refractory end-stage glaucoma cases.

Previous, smaller, limited studies have shown promising results of MPTSCPC, with a good efficacy and side effect profile for advanced stage glaucoma.^{11,22–27} The purpose of our longitudinal study is to significantly expand on previous smaller studies by using a larger data set of patients from multiple centers, as well as a broad spectrum of glaucoma severity, to show the safety and efficacy of this novel application of micropulse laser in cycloablative procedures.

MATERIALS AND METHODS

Study Design

In this retrospective, longitudinal study, we included all patients who underwent MPTSCPC with P3 probe for the treatment of any type and stage of glaucoma between the dates April 2015 and May 2017. Before the initiation of the study approval was obtained from the Institutional Review Board of Tulane University School of Medicine, granting a retrospective review exempt status. The research was conducted in accordance with the tenets set forth in the Declaration of Helsinki. All patient identifiers were removed while analyzing the data, in compliance with HIPAA (Health Insurance Portability and Accountability Act of 1996) regulations. The patient data were collected from 5 different clinical sites (Tulane Study Group—details in acknowledgment).

Laser Intervention

A transscleral diode laser, the Cyclo G6 laser system (MPTSCPC; IRIDEX IQ810 Laser Systems, CA) with a P3 probe, was used for this procedure. The laser settings used were standardized at: power 2000 mW, micropulse “ON” time 0.5 ms, micropulse “OFF” 1.1 ms, and duty cycle at 31.33%. These laser settings are also similar to previously published studies.

All procedures were performed in the operating room with the patient under monitored anesthesia care, with addition of retrobulbar/peribulbar block (1:1 mixture of Carbocaine and Marcaine) for increased patient comfort during the procedure. The P3 probe was seated at the limbus over the conjunctival surface; the probe is designed to permit accurate positioning of the fiberoptic tip at 3 mm posterior to the limbus perpendicular to the globe. It was then moved in a slow and steady, continuous manner, clockwise and counterclockwise, beginning at the superior or inferior half. A 180-degree arc was initially done, and subsequently the remaining 180 degrees are filled in to complete the treatment session. The 3 and 9 o'clock positions were left untreated to avoid ciliary neurovascular structures. The laser was delivered over 90 to 120 seconds to each arc at the physician discretion. Topical steroid and cycloplegic drops were used postoperatively, and the eye was not patched. All patients received prednisolone drops 1% 8 times a day for 1 week, 4 times a day for 3 weeks. No one needed oral prednisone. Inflammation resolved in all patients in <1 month. No pressure reducing drops were used preoperatively.

The patients were seen on day 1, 1 week, 1 month, 3 months, 6 months, and every 3 months thereafter. At every visit, the following data were recorded: vision, IOP, and slit lamp examinations, especially the amount of postoperative inflammation and the number of medications. The inflammation was graded using the standardization of uveitis for grading inflammation in the anterior and vitreous chambers.

Data

The following variables were analyzed: age, sex, race, type of glaucoma, duration of glaucoma, any other ocular diagnosis, past ocular surgeries, visual acuity (VA), IOP, oral and topical IOP medications, lens status, visual fields, optical coherence tomography of disc, type of anesthesia, surgery setting, laser settings, complications, pain (yes vs. no) repeat procedures, need for further glaucoma surgery. All specific patient identifiers were removed.

Surgical Success

Surgical success for the purposes of this study was defined based on multiple patient outcomes, including IOP, VA glaucoma medications, need for repeat micropulse procedure, and need for another glaucoma procedure. The successfully treated eye had an IOP defined as IOP > 6 or < 18 mm Hg or 20% reduction in IOP from baseline. Failure was defined as: (1) IOP < 6 mm Hg (with hypotony maculopathy) or > 18 mm Hg with or without medications, (2) vision loss of (light perception) or loss of 3 or more lines attributable to laser procedure, and (3) necessity of further glaucomatous surgical intervention. The conservative composite definition of total success in our study required that the eye fulfill multiple definitions of success, including IOP, VA and no further needs for another glaucoma surgery. Target pressures based on severity were not obtained from chart review; surgical success was defined purely on the basis of IOP reduction and not based on target IOP based on severity.

Statistical Analysis

IOP was compared relative to preoperative baseline at 7 postoperative time points (1 d, 1 wk, 1 mo, 3 mo, 6 mo, 9 mo, 12 mo/last follow-up) using repeated measures analysis of variance and paired *t* tests. Changes in logMAR acuity were assessed by the Wilcoxon signed-rank test. Freedom from repeat micropulse procedures was evaluated using the Kaplan-Meier product-limit method with 95% confidence intervals (CIs) determined by Greenwood formula.²⁸ Multivariable logistic regression was applied to identify significant independent predictors of total success by testing several patient demographic and baseline variables and with odds ratios and 95% CIs reported and we used a generalized estimating equations approach to account for multiple eyes within the same patient.²⁹ IOP is summarized using means and SDs whereas VA and duration of follow-up are described by median values and interquartile range (IQR). Two-tailed values of *P* < 0.05 were considered statistically significant with use of Bonferroni adjustment to account for multiple variables being tested. Statistical analysis was performed using Stata software (release 13.1; Stata Corporation, College Station, TX). Power analysis indicated that the sample size provided 90% power to detect mean changes in IOP from baseline to last follow-up of 20% using repeated measures analysis of variance, and to identify significant predictors of total success using the odds ratio as the effect size based on multivariable logistic regression (version 7.0, nQuery Advisor; Statistical Solutions, Cork, Ireland).

RESULTS

One hundred ninety-seven eyes of 161 patients, underwent the MPTSCPC treatment during the study period. The mean age was 73 years (SD = 12 y; range, 19 to 96 y) and there were more males (55%). Tables 1 and 2 summarize the demographic and clinical characteristics of the patients in our study, as well as postsurgical outcomes. Although primary open-angle glaucoma (POAG) accounted for majority of the study [141 patients (88%)], the study included 8 patients (5%) with neovascular glaucoma (NVG) and 12 patients that had other types of glaucoma [uveitic glaucoma (4), chronic angle closure glaucoma (4), penetrating keratoplasty glaucoma (3), and iridocorneal endothelial syndrome (1)]. Subgroup analysis of the individual diagnosis in the other category was not performed because of the low numbers. One hundred fifty-two patients had

TABLE 1. Demographic and Clinical Characteristics of Cohort

Age (SD) (y)	73 (12)
No. patients/eyes	161/197
Sex (%)	55 male, 45 female
Eye laterality	94 left, 103 right
Race [n (%)]	White 81 (50), Hispanic 55 (34), black 25 (16)
Previous laser treatment [n (%)]	89 (55)
Type of glaucoma [n (%)]	POAG 141 (88), NVG 8 (5), other 12 (7)

NVG indicates neovascular glaucoma; POAG, primary open-angle glaucoma.

MPTSCPC alone, whereas 25 patients from 1 study site had MPTSCPC along with additional procedures; these included 14 phaco/iStent, 9 phacoemulsification with intraocular lens implantation; 2 ab interno trabeculotomy with Kahook dual blade. Eighty-nine (55%) patients had previous laser treatment. Previous laser treatment included either selective laser trabeculoplasty or argon laser trabeculoplasty for (POAG) patients.

The median follow-up time was 12 months (IQR, 6 to 14 mo; range, 3 to 25 mo). Mean IOP decreased from 21.5 to 15.8 mm Hg at last follow-up ($P < 0.001$). Median number (IQR) of glaucoma medications decreased from 3 to 2 at the last postoperative period ($P < 0.001$, Wilcoxon signed-rank test). Ten percent had preoperative systemic medications (Diamox) compared with 8% at the last postoperative period. Median logMAR VA was 0.4 preoperative and 0.3 postoperative ($P = 0.65$, Wilcoxon signed-rank test). Sixty-three percent (123 patients) reported pain during the procedure, whereas 45% (86 patients) reported pain during the immediate postoperative period. Postoperative inflammation 47% (91 patients), was successfully treated with prednisolone taper over as described in the Materials and methods section.

Postoperative mean IOP at each time point is significantly lower than preoperative baseline IOP (all $P < 0.001$), as shown in Figure 1. The total success rate for our study is 71%, as shown in Figure 2, which includes patients that had an IOP < 18 (or 20% reduction) with no hypotony, did not need to have another glaucoma procedure, and did not lose 3 or more lines in VA. The Kaplan-Meier curve, Figure 3, estimates indicate that 97% of eyes were free from repeat MPTSCPC at 3 months and 90% free

TABLE 2. Postsurgical Outcomes

	Preoperative	Postoperative Outcomes
IOP: mean \pm SD (mm Hg)	21.5 \pm 9	15.8 \pm 6
Median logMAR VA (IQR)	0.4 (0.2-1.0)	0.3 (0.2-1.0)
Number topical medications median (IQR)	3 (1-4)	2 (1-3)
Systemic glaucoma medications (% patients) [n (%)]	24 (10)	21 (8)
Median follow-up (IQR) (mo)	12 (IQR, 6-14) min-max: 3-25	
Intraoperative complications		0
Postoperative complications [n (%)]	4 (2) with CME, resolved	

CME indicates cystoid macular edema; IQR, interquartile range; max, maximum; min, minimum; VA, visual acuity.

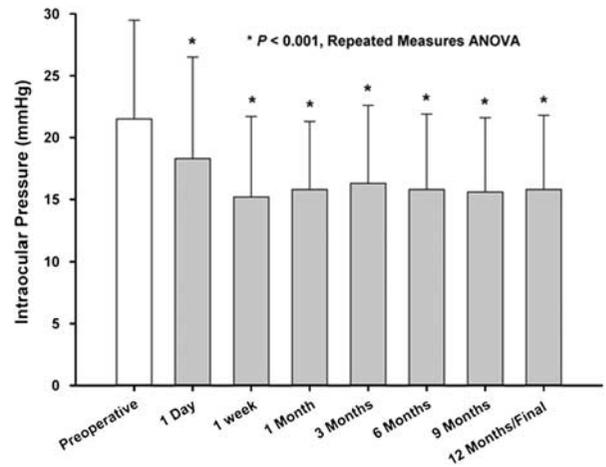


FIGURE 1. Postoperative mean intraoperative pressure at each time point is significantly lower than preoperative baseline (all $P < 0.001$, as represented by the asterisks). ANOVA indicates analysis of variance.

at 12 months (95% CI, 86%-94%); 16 of the 17 repeat micropulse procedures occurred before 12 months and 1 eye needed reintervention 14 months after initial MPTSCPC.

Twenty-five patients from 1 study site had multiple concurrent procedures; this included 14 phaco/iStent, 9 phaco; 2 ab interno trabeculotomy with Kahook dual. This subgroup had a higher total success rate (22/25=88%) compared with the total success in the study (71%). In comparison, patients with POAG had a total success rate of 73% (126/172) and those with previous glaucoma surgery had a success rate of 80% (58/73). The 25 patients with multiple concurrent procedures had a total success rate 20% higher than the others (22/25=88% vs. 117/172=68%, $P = 0.05$, Fisher exact test). The 25 eyes with multiple concurrent procedures had significantly lower preoperative IOP

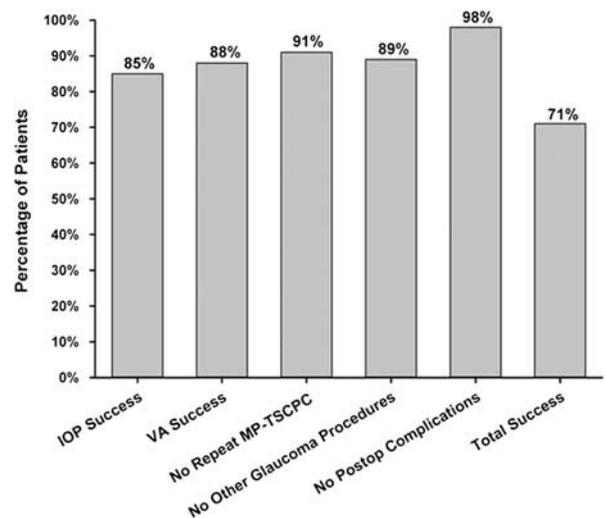


FIGURE 2. Eighty-five percent of all patients had an intraoperative pressure (IOP) ≥ 6 and ≤ 18 , 88% did not lose ≥ 3 lines in visual acuity, and 89% did not have any other glaucoma procedures. The criteria to be met for total success (71%) include IOP, no other glaucoma procedures, and no significant change in visual acuity (3 lines or loss of light perception). MPTSCPC indicates micropulse transscleral cyclophotocoagulation.

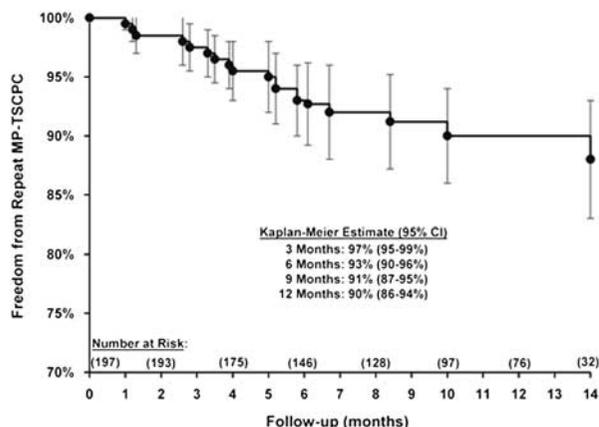


FIGURE 3. Kaplan-Meier curve for all 197 eyes (17 events or steps along the curve). Errors bars denote 95% confidence intervals (CIs), as determined by Greenwood formula. The numbers at risk shown in parentheses at the bottom are the numbers of eyes with continued follow-up that did not require any repeat micropulse transscleral cyclophotocoagulation (MPTSCPC).

than those without concurrent procedures (17 ± 6 vs. 22 ± 9 mm Hg, $P = 0.002$). If we adjust for preoperative IOP, we find that it is the lower preoperative IOP rather than the concurrent procedures that explain the higher success rate. The multivariable logistic model indicates that after controlling for preoperative IOP, there is no significant advantage regarding total success for those patients having multiple concurrent procedures ($P = 0.12$). Thus, the higher success rate among this subgroup from a single center is attributed to their having a lower baseline IOP rather than pressure lowering effects of the concurrent procedures.

Among the 17 eyes that required retreatment, the median time to retreatment was 13 months (IQR, 6 to 15 mo). When we considered several baseline variables to assess whether these 17 had greater glaucoma severity and the only variable that was significantly higher than the eyes not needing MPTSCPC retreatment was their preoperative IOP (27 ± 7 vs. 21 ± 8 mm Hg, $P = 0.004$). A multivariable Cox regression analysis was performed to determine factors associated with a higher monthly hazard for requiring retreatment and the only variable is preoperative IOP (hazard ratio = 1.08; 95% CI, 1.05-1.12). Receiver-operating characteristic curve analysis was performed to assess how predictive preoperative IOP is, regarding the likelihood for repeat MPTSCPC and the area under the curve indicated a strong relationship (area under the curve = 0.745; 95% CI, 0.620-0.855; $P = 0.001$).

Multivariable logistic regression identified 3 significant independent predictors of total success: diagnosis ($P = 0.011$), previous glaucoma surgery ($P = 0.003$), and other concurrent procedures ($P = 0.013$). Patients with POAG had a higher likelihood of total success than NVG or other diagnoses (odds ratio = 3.4; 95% CI, 1.4-8.9). Patients with previous glaucoma surgery had a significantly higher odds of total success (odds ratio = 2.9; 95% CI, 1.4-6.0) as did patients with concurrent procedures (odds ratio = 4.0; 95% CI, 1.2-14.2). Multivariable analysis indicated that age ($P = 0.98$), sex ($P = 0.76$), race ($P = 0.83$), lens status ($P = 0.75$), previous laser treatment ($P = 0.10$), previous ocular surgery ($P = 0.68$), and baseline IOP ($P = 0.11$) were not significantly associated with total success.

Complications included 4 cases of cystoid macular edema (CME), which eventually resolved with an extended taper of postoperative prednisolone drops. There was no

development of corneal edema, prolonged hypotony, phthisis bulbi, or mydriasis.

DISCUSSION

This retrospective longitudinal cohort from multiple independent eye clinics that made up the Tulane Study Group revealed a total success of 71% at final follow-up, which is similar to other published studies.^{11,22,23,26,27} Mean IOP was significantly reduced from 22 to 16 mm Hg at final follow-up, which on average, represents a 27% reduction. Our results are in agreement with previous studies showing very rapid IOP lowering, as early as postoperative day 1.¹¹ This has been attributed both to the possibility of increased uveoscleral outflow, as well as decreased aqueous production.²⁰ Our group did not perform any further experiments to clarify this mechanism. We have also shown that this procedure is safe and effective mostly for POAG, as there was only a 2% complication rate (only CME in our study).

Previously, cyclodestructive procedures such as cyclo-cryotherapy and CPC were reserved for poorly controlled glaucoma and limited visual prognosis. The continuous transscleral cyclophotocoagulation has been mainly retained for end-stage glaucoma due to the high rate of potential complications. Some of the complications associated with cyclodestructive procedures using laser include vision loss, corneal edema, pupillary distortion, cystoid macula edema, and hypotony.^{3,7-10} However, the thermal localization of energy by the micropulse laser offers the possibility minimizing excess tissue disruption, as shown through histologic specimens of traditional CPC.³⁰ Our study only showed 4 cases of CME, which resolved without any loss of VA. This low complication rate is similar to other smaller published studies.^{11,22-27} The minimal delivery of energy during the procedure resulted in minimal pain, with less than half complaining of some degree of pain. The minimal risks and pain allows the possibility of performing this procedure in an in-office setting, rather than an outpatient operating room, minimizing both time and cost.

Twenty-five patients in our study had multiple concurrent procedures; this included 14 phaco/iStent, 9 phaco; 2 ab interno trabeculectomy. This subgroup had a high total success rate (22/25 = 88%). However, after adjusting for differences in baseline mean IOP between patients with and without multiple concurrent procedures, the groups are no longer different with respect to total success. The 25 eyes with multiple concurrent procedures had significantly lower preoperative IOP than those without concurrent procedures (17 ± 6 vs. 22 ± 9 mm Hg, $P = 0.002$). Current literature has very little to offer in regards to surgical outcomes when minimally invasive glaucoma surgery procedures are combined with glaucoma procedures that work with a different mechanism (eg, iStent that improves the conventional outflow+micropulse that reduces aqueous production). This concept deserves further studies even though in the current paper the results are not significant.

Retreatment was needed in 17 eyes with a median time to retreatment of 13 months (IQR, 6 to 15 mo). Preoperative IOP in this subgroup (27 ± 7 vs. 21 ± 8 mm Hg, $P = 0.004$) was found to be significantly higher and the only variable that was significantly higher than the eyes not needing MPTSCPC retreatment.

Our study found that IOP was not a predictor of total success but it is a predictor of success in repeat MPTSCPC. Note that the total success was defined as a composite—of IOP, vision, and whether or not additional glaucoma

surgery was required. Total success rate was 71% (this pertains to 139 of 197 eyes; that is 58 eyes failed something), that is 71% passed all 3 metrics above. And based on all of the variables (there are many) that we included as candidates in the multivariable analysis of total success—baseline IOP was not retained as an independent predictors of total success. However, IOP was found to be an independent predictor in patients who underwent repeat MPTSCPC by multivariable analysis. Note that the multivariable analysis of repeat MPTSCPC is based on a multivariable Cox time-to-event model whereas the multivariable analysis of total success is based on multivariable logistic KM curve and is an estimate of repeat MPTSCPC. On the basis of the data, the KM model estimates that 90% of patients will be free of repeat MPTSCPC at 12 months.

Our study has several limitations. Retrospective nature of study, limited follow-up (3- to 12-mo follow-up) and the multicenter study design are some of the limitations. Also, most of the patients in the study had POAG. The number of patients with secondary glaucoma (NVG, uveitis glaucoma, penetrating keratoplasty with glaucoma, etc.) constituted <20% of the total eyes. Furthermore, our study did not include pediatric patients. However, our study showed a similar success rate compared with other smaller studies, which ranged from 40% to 80%.^{22,23,26,27} Our complication rate was also similar to published studies, which was <10%.^{22,23,26,27} This new method of delivery may be of help in patients who cannot take medications or delay incisional surgery. Furthermore, patients at high risk of complications from incisional surgery can potentially use MPTSCPC as an alternative. Given the safety profile of this device, this can also complement prior tube shunt or filtration procedures. Our large retrospective review has provided further evidence that MPTSCPC can be a safe (2% complication rate) and effective (71%) option in the arsenal of glaucoma treatment for patients primarily, with POAG. Further studies are needed to evaluate its long-term efficacy with comparisons to other surgical treatment options and when combined with other surgical procedures in other types of glaucoma.

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