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Efficacy of selective laser trabeculoplasty in primary open-angle glaucoma eyes with functional versus organic blockage of Schlemm's canal

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Background: *The European Glaucoma Society recommends that selective laser trabeculoplasty (SLT) be considered as a first-line treatment option for patients with mild or moderate primary open-angle glaucoma (POAG) or for those who have not responded well to medications.*

Purpose: *To assess the efficacy of POAG treatment with SLT based on examination of the function of Schlemm's canal (SC)*

Methods: *This paper presents the results of clinical studies and one-month dynamic follow-up of 38 POAG patients (52 eyes) who underwent SLT with a Tango Reflex YAG/SLT laser (Ellex, USA) at the VISUS clinic (Zaporizhzia). Of the 38 patients, 18 (47.37%) were males and 20 (52.63%) females. Patient age ranged from 58 to 85 years (mean age ± standard deviation, 69 ± 9.9 years).*

Results: *There was a significant difference in the response to SLT between eyes with a functional blockage and those with an organic blockage of SC. In the former eyes, true intraocular pressure (P_0) decreased from 25.66 ± 0.41 mmHg before SLT to 19.2 ± 0.24 mmHg, outflow facility coefficient increased by 40%, and Becker's coefficient decreased by 46.63% at 1 month after SLT ($p < 0.05$). In eyes with an organic blockage of SC, P0 changed from 27.69 ± 0.51 mmHg before SLT to 27.64 ± 0.49 mmHg at 1 week, and even increased to 28.75 ± 0.52 mmHg at month 1 after SLT ($p > 0.05$), and tonography characteristics did not change.*

Conclusion: *The current study demonstrated that the success rate of SLT in eyes with POAG was 69.2%. The success rate, however, may reach 100% (with a mean percentage IOP reduction of 25.18%, 40 percent increase in the outflow facility coefficient, and 46.63 percent decrease in the Becker's coefficient) if SLT is performed only in POAG eyes with a functional blockage of SC. If established, the functional state of SC may be used for determining indications and contraindications for SLT in POAG.*

Keywords:

primary open-angle glaucoma, intraocular pressure, selective laser trabeculoplasty, functional state of Schlemm's canal

Introduction

Intraocular pressure (IOP) reduction is essential for preservation of visual function in glaucoma and is achieved commonly by medication therapy, laser or surgical treatment. IOP-lowering medications are a common first-line treatment for glaucoma, but patient compliance may be poor [1]. Most authors note that IOP should be lowered to the target pressure, which in turn depends on many factors [2], including the state of cornea and sclera. Peretiagin [3] and Dmitriev and colleagues [4] concluded that absolute values of target pressure required for stabilization of primary open-angle glaucoma (POAG) in patients with high corneoscleral rigidity were 10.7% lower than those for patients with low corneoscleral rigidity.

Recently, increased attention has been given to laser IOP-lowering techniques such as selective laser trabeculoplasty (SLT) which is based on the principle of selective photothermolysis.

The major advantages of laser intervention are the absence of serious intraoperative and postoperative complications, relative painlessness, non-invasiveness and possibility of outpatient intervention [5, 6]. SLT is a safe and effective modality for lowering IOP in patients with POAG. The European Glaucoma Society recommends that SLT be considered as a first-line treatment option for patients with mild or moderate POAG or for those who have not responded well to medications. In addition, SLT may be combined with medication therapy for better IOP control [5].

The literature reports on (a) numerous ways by which SLT may be performed, (b) the mechanism by which SLT lowers IOP, and (c) surgery combined with SLT [7, 8, 9, 10]. Unfortunately, the efficacy of laser treatment does not always meet the needs of patients, and this treatment does not always provide a sustained and prolonged IOP-lowering effect [11].

Indications for SLT are rather general (open anterior chamber angle (ACA) and moderately increased IOP [12]), which we believe somewhat limits its wider use in clinical practice. It is the absence of a clear idea on indications and contraindications of laser trabeculoplasty which (a) causes a lack of trust among specialists in this method of treatment for glaucoma and (b) makes the current study important.

The purpose of this study was to assess the efficacy of POAG treatment with SLT based on examination of the function of the Schlemm's canal (SC).

Methods

This paper presents the results of clinical studies and one-month dynamic follow-up of 38 POAG patients (52 eyes) who underwent SLT at the VISUS clinic (Zaporizhzhia), the clinical home of the Department of Ophthalmology at Zaporizhzhia State Medical and Pharmaceutical University.

Inclusion criteria were the presence of POAG, a widely open ACA at gonioscopy, and mild or moderately elevated IOP. Appropriate informed consent was obtained from all patients.

The most common comorbidity was hypertensive disease (35 patients or 92.11%), followed by atherosclerosis (25 patients or 65.79%), coronary heart disease (18 patients or 47.37%), and cardiac insufficiency (10 patients or 26.32%).

Of the 38 patients, 18 (47.37%) were males and 20 (52.63%) were females. Patient age ranged from 58 to 85 years (mean age ± standard deviation, 69 ± 9.9 years). Of the affected eyes, 14 (26.92%) had POAG stage I, 15 (28.85%), POAG stage II, 13 (25%), POAG stage III, and 10 (19.23%), POAG stage IV. At the initiation of the dynamic follow-up, IOP ranged from 23 to 31 mmHg (mean IOP ± standard deviation, 26.5 ± 2.3 mmHg), irrespective of the stage of the process. At the time of inclusion in the study, most patients were on topical IOP-lowering medications. Prostaglandin analogues were most commonly used (15 eyes or 28.85%), followed by beta-blockers (12 eyes or 23.08%), carbonic anhydrase inhibitors (4 eyes or 7.69%), and alpha-2 selective adrenergic agonists (4 eyes or 7.69%). In addition, combination drugs were used in 7 eyes (13.56%). In addition, glaucoma process was initially established in 10 eyes (19.23%), and these eyes were not administered IOP-lowering therapy.

All patients underwent standard eye examination (visual acuity assessment and slit-lamp biomicroscopy and indirect ophthalmoscopy (model SL-1E; Topcon, Tokyo, Japan)), gonioscopy with a Latina SLT Gonio lens (Ocular Instruments, Bellevue, WA), and pneumatonometry and tonography (Model 30 Classic Pneumatonometer, Reichert Ophthalmic instruments, Depew, NY).

Of note that tonography with this pneumatonometer enables assessing the major parameters of ocular hydrodynamics such as the true IOP (P_0), outflow facility coefficient (C), and Becker's coefficient (BC), which is required for calculating the aqueous outflow per minute (F).

In order to determine the functional state of Schlemm's canal (i.e., whether there was a functional or organic blockage of Schlemm's canal), tonography was performed before and one hour after the glycerol ascorbate test. Changes in the outflow facility coefficient (C) were assessed. An increase in the outflow facility coefficient at 1 hour after the glyceryl ascorbate (1.5 g per 1 kg body weight) test indicated the presence of a functional blockage of Schlemm's canal, whereas no change in the coefficient indicated the presence of organic changes in the canal. Therefore, even an insignificant increase at 1 hour after the glyceryl ascorbate test indicated the presence of functional changes in Schlemm's canal, and eyes with such a decrease were categorized as those with functional blockage of Schlemm's canal.

In order to determine normal tonography values for the Model 30 Classic Pneumatonometer, we examined 20 patients (40 eyes; age, 59 to 78 years; mean age ± standard deviation, 68.5 ± 13 years) with a cataract without elevated IOP or other signs of glaucoma process.

In all eyes with POAG, SLT was performed using a Tango Reflex YAG/SLT laser (Ellex, USA) and Latina SLT Gonio lens, with 50-60 laser spots in 180-270 degrees (Fig. 1). For each patient, the laser was set at the level required to generate minimum bubbles (mean level, 0.8 mJ). Patients received epibulbar anesthesia with proxymetacaine hydrochloride before the laser procedure and chloramphenicol 0.25% after the laser procedure. Bromfenac 0.09% was used to prevent inflammation after the procedure.

This study included human participants, was approved by the local bioethics committee and adhered to the Declaration of Helsinki, European Convention on Human Rights and Biomedicine, and relevant laws of Ukraine. Appropriate informed consent was obtained from patients.

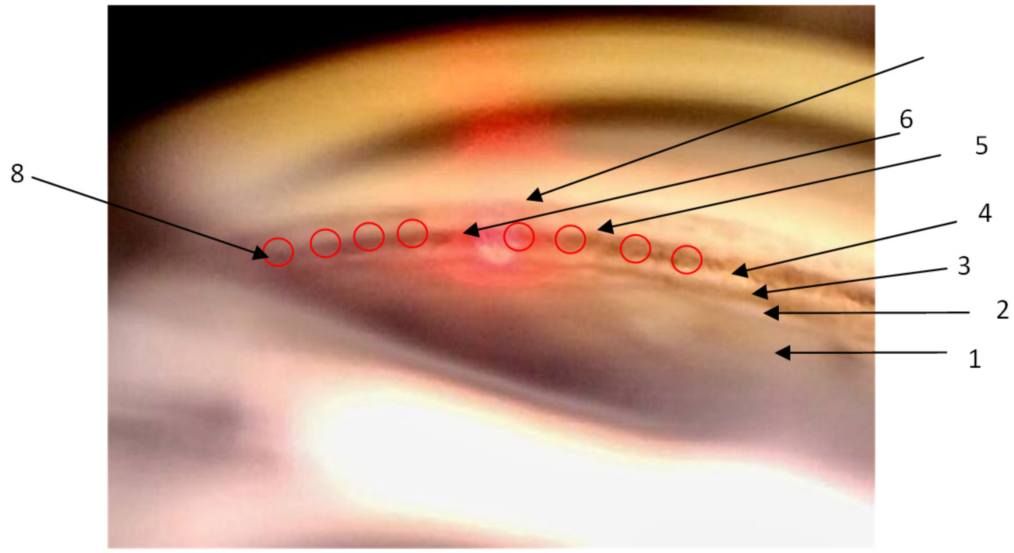

Fig. 1. Photograph of the anterior chamber angle. Note: 1, iris; 2, ciliary body; 3, scleral spur; 5, trabecular apparatus; 6, laser ray; 7, Schwalbe's ring; 8, target sites for subsequent laser application

Microsoft Excel 2017 and Statistica for Windows 10.0 (Stat Soft Inc., Tulsa, OK, USA) were employed for statistical analyses. Normally distributed data are presented as means and standard deviation (SD). Student t test and Pearson chi-square test were used to evaluate the level of significance. The level of significance $p \leq 0.05$ was assumed.

Results

The preoperative hydrodynamic characteristics (particularly, the outflow facility coefficient reflecting the state of the drainage system) in the glaucomatous eye were of particular interest. Table 1 presents the results of electronic tonography and their comparison with reference normal values.

In eyes without glaucoma, tonography values were within the normal range, with a mean IOP ± SD of 19.06 ± 0.26 mmHg and a mean outflow facility coefficient ± SD of 0.38 ± 0.03 mm^3/min/mmHg. In eyes with glaucoma and eyes with newly detected glaucoma, true IOP increased to 25.18 ± 0.76 mmHg, and 26.80 ± 0.34 mmHg, respectively, in the presence of topical IOP-lowering therapy. In addition, there was a substantial reduction in the outflow facility coefficient to 0.1 ± 0.02 and 0.16 ± 0.02 mm^3/min/mmHg in eyes treated and not treated with IOP-lowering therapy, respectively.

Of note that electronic or conventional tonography allows assessing the state of the aqueous outflow from the eye, but provides no information on the state of ocular drainage system proper (namely, the state of Schlemm's canal), which is important for selecting further treatment strategy, and especially for determining indications for SLT. That is why, in order to assess the state of SC, tonography was performed before and one hour after the glycerol ascorbate test to assess the outflow facility coefficient (C). An increase in the outflow facility coefficient at 1 hour after the glyceryl ascorbate (1.5 g per 1 kg body weight) test indicated the presence of functional blockage of SC, whereas no change in the coefficient indicated the presence of organic changes in the canal.

Table 1. Ocular hydrodynamic characteristics in eyes with primary open-angle glaucoma and controls (mean ± standard deviation)

		P_0 (mmHg)	Outflow facility coefficient (mm^3/min/mmHg)	F (mm^3/min)	F (mm^3/min)
Control group, n=40		19.06±0.26	0.38±0.03	3.49±0.26	57.17±4.2
Eyes with glaucoma	not treated with topical IOP-lowering therapy, n = 10 (19.23%)	25.18±0.76 *	0.1±0.02 *	4.1±0.35	345±84.6 *
	treated with topical IOP-lowering therapy, n = 42 (80.77%)	26.81±0.34 ◊	0.16±0.02 ◊	2.52±0.3 ◊	475±109 ◊

Note: n, number of eyes; P_0, true intraocular pressure; F, aqueous outflow per minute; BK, Becker's coefficient; *, significant difference (p < 0.05) between control eyes and glaucoma eyes not treated with topical IOP-lowering therapy; ; ◊, significant difference (p < 0.05) between control eyes and glaucoma eyes treated with topical IOP-lowering therapy.

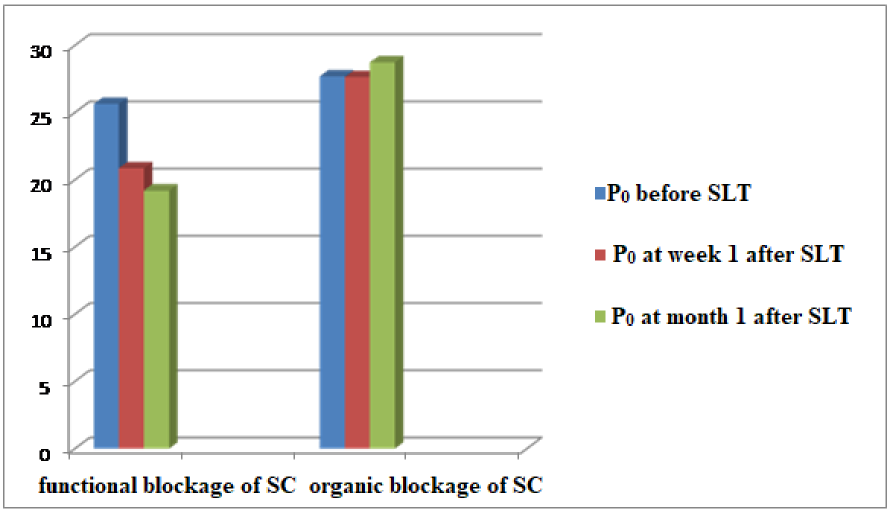

Fig. 2. True intraocular pressure (P0) values in eyes with a functional blockage of Schlemm's canal (SC) versus those with an organic blockage of SC before SLT and at week 1 and month 1 after SLT

Thereafter, all study eyes were divided into two groups based on the results of the glyceryl ascorbate test (Table 2): group 1 (36 eyes, 69.23%) with a functional blockage of Schlemm's canal, and group 2 (16 eyes, 30.77%) with an organic blockage of SC.

In eyes with a functional blockage of SC, taking glyceryl ascorbate resulted in a statistically significant reduction in IOP from з 26.38 ± 0.39 mmHg to 18.36 ± 0.29 mmHg with a significant increase in the outflow facility coefficient (from 0.19 ± 0.02 to 0.32 ± 0.03 mm3/min/mmHg, $p < 0.01$) (Table 2). In eyes with an organic blockage of SC, it, however, resulted in no increase in the outflow facility coefficient, and no reduction in the IOP (with a change from 27.75±0.43 mmHg to 27.18±0.42 mmHg, $p > 0.05$).

It is noteworthy that there was no significant difference in IOP between groups at baseline (although the mean value in group 1 was close to that in group 2, 26.38 ± 0.39 and 27.75±0.43 mmHg, respectively, $p > 0.05$). However, a significant difference in the outflow facility coefficient between group 1 and group 2 was observed at baseline (0.19 ± 0.021 and 0.11 ± 0.008 mm^3/min/mmHg, respectively, $p < 0.05$), and increased substantially after patients took glyceryl ascorbate (0.32 ± 0.039 mm^3/min/mmHg and 0.13 ± 0.019 mm3/min/mmHg, respectively, $p < 0.05$).

All affected eyes underwent the SLT procedure as described above. After SLT, there was a significant difference in the response between eyes with a functional blockage of SC and those with an organic blockage of SC (Fig. 2).

Thus, in the former eyes, true IOP decreased from 25.66 ± 0.41 mmHg to 20.87 ± 0.33 mmHg at 1 week, and to 19.2 ± 0.24 mmHg at 1 month after SLT ($p < 0.05$ for both comparisons to baseline) without a change in IOP-lowering therapy. Laser trabeculoplasty, however, did not result in an improvement in true IOP in eyes with an organic blockage of SC. Thus, in this group, true IOP

Table 2. True intraocular pressure and outflow facility coefficient values in eyes with a functional blockage of Schlemm's canal versus eyes with an organic blockage of Schlemm's canal before and after the glycerol ascorbate test (mean ± standard deviation)

Functional or organic blockage of Sclemm's canal	Number (percent-tage) of eyes	Results of the glycerol ascorbate test			
		P_0 (mmHg)		C (mm^3/min/mm)	
		Before test	After test	Before test	After test
Functional blockage (group 1)	36 (69.23%)	26.38±0.39	18.36±0.29 *	0.19±0.021	0.32±0.039 *
Organic blockage (group 2)	16 (30,77%)	27.75±0.43	27.18±0.42 #	0.11±0.008 #	0.13±0.019 #

Note: P_0, true intraocular pressure; C, outflow facility coefficient; *, significant difference ($p < 0.05$) compared to baseline values; #, significant difference ($p < 0.05$) between groups

Table 3. Outflow facility coefficient, aqueous outflow per minute and Becker's coefficient values in eyes with a functional blockage of Schlemm's canal versus eyes with an organic blockage of Schlemm's canal before selective laser trabeculoplasty (SLT) and at 1 week and 1 month after SLT (mean ± standard deviation)

Functional or organic blockage of Schlemm's canal		**C (mm³/min/mmHg)**	**F (mm³/min)**	**BC (P0/C)**
Functional blockage (36 eyes)	before SLT	0.18±0.014	3.1±0.41	180.4±27.12
	1 week after SLT	0.22+0.019 *	2.83±0.26 *	92.55±6.81 *
	1 month after SLT	0.3±0.015 *	2.09±0.27 *	96.07±6.74 *
Organic blockage (16 очей)	before SLT	0.11±0.008	0.98±0.16	973±238
	1 week after SLT	0.12±0.018	0.87±0.15	1005±227
	1 month after SLT	0.11±0.011	0.99±0.17	1112±273

Note: C, outflow facility coefficient; F, aqueous outflow per minute; BC, Becker's coefficient; *, significant difference ($p < 0.05$) compared to baseline values

changed from 27.69 ± 0.51 mmHg before SLT to 27.64 ± 0.49 mmHg at 1 week, and even increased to 28.75 ± 0.52 mmHg at month 1 after SLT ($p > 0.05$).

The values of the outflow facility coefficient, aqueous outflow per minute and Becker's coefficient in eyes with a functional blockage versus those with an organic blockage of SC before and after SLT are presented in Table 3.

With a reduction in IOP in eyes in group 1, there was an improvement in all ocular hydrodynamic indices (especially the outflow facility coefficient and Becker's coefficient), which indicated a reduction in the resistance to aqueous outflow in eyes with a functional blockage of SC. Thus, in this group, at month 1 after SLT, the outflow facility coefficient increased by 40% (from 0.18 ± 0.014 to 0.3 ± 0.015 mm3/min/mmHg, $p < 0.05$), and Becker's coefficient decreased by 46.63% (from 180.4 ± 27.12 to 96.07 ± 6.74, $p < 0.05$) compared to baseline values.

In addition, no substantial changes in the outflow facility coefficient at week 1 and month 1 compared to baseline values (0.11±0.008 mm^3/min/mmHg before SLT and 0.12 ± 0.018 and 0.11 ± 0.011 mm^3/min/mmHg, respectively, at week 1 and month 1) were observed in eyes with an organic blockage of SC. The aqueous outflow per minute and Becker's coefficient in this group also did not change substantially after SLT. Subsequently, all study eyes with an organic blockage of SC underwent surgery.

Discussion

At present, SLT is a standard therapy for POAG, and may be used as an adjunct to IOP-lowering drug therapy or as a first-line treatment in patients with mild to moderate IOP in eyes with newly detected glaucoma or as an alternative treatment for patients who experience side effects with IOP-powering drugs [5, 12]. POAG, low-tension glaucoma, pigment glaucoma and pseudoexfoliation glaucoma may be treated with laser [2, 13].

During SLT, the laser targets pigmented structures of the trabecular meshwork (and thus improves aqueous filtration) and does not damage the non-pigmented cells and other non-pigmented trabecular structures [14], thus improving aqueous outflow and leading to IOP reduction. Multiple studies reported on an 18-40 percent reduction in IOP after SLT [15-17]. The success rate of SLT varies from 48.72% to 74.2% [5, 8, 17, 18] which somewhat limits its wider use in clinical practice. Transparent ocular media and good visualization of the trabecula are the current requirements for laser trabeculoplasty.

The results of our studies indicated that the success rate of SLT depends also on the functional state of Schlemm's canal. It is known that, in the eye with glaucoma, ocular hydrodynamic abnormalities develop slowly and initially represent functional changes which may regress with adequate treatment, which is confirmed by a high success rate of IOP-lowering drug therapy for early glaucoma. The state of the trabecular meshwork and Schlemm's canal plays a key role in aqueous outflow. The formation of a functional blockage gives rise to the formation of an organic blockage of SC [19]. It is easy to understand that, at the phase of an organic blockage, when commissures develop in the lumen of Schlemm's canal, drug therapy and trabeculoplasty become ineffective in lowering IOP.

Our findings completely confirm this statement. Thus, SLT was found to be ineffective in the eyes in which an organic blockage of SC was detected, which was indicated by the absence of improvement in IOP with time after SLT in this group (before SLT and at 1 week and 1 month after SLT, P0 was 27.69 ± 0.51 mmHg, 27.64 ± 0.49 mmHg, and 28.75 ± 0.52 mmHg, respectively ($p > 0.05$), and C was 0.11 ± 0.008 mm^3/min/mmHg, 0.12 ± 0.018 mm^3/min/mmHg and 0.11 ± 0.011 mm^3/min/mmHg, respectively). However, in all eyes in which a functional blockage of SC was diagnosed, SLT was a success, with a mean percentage IOP reduction of 25.18% in the presence of an improvement in all ocular hydrodynamic characteristics. Thus, over a one-month follow-up, the outflow facility coefficient increased by 40%, and the Becker's coefficient (which characterizes the state of trophic processes in the eye), decreased by 46.63%.

We found SLT to be effective without a change in the topical drug regimen in 32/52 affected eyes (62.9%), which is in agreement with the findings of others [8, 17] on the success rate of SLT. The success rate, however, may reach 100% if SLT is performed only in eyes with a functional blockage of SC, which is indicated by our study.

It is necessary to dwell on the finding of a difference in the outflow facility coefficient between the groups. At baseline, the mean IOP for group 1 was close to that for group 2 (26.38 ± 0.39 mmHg and 27.75±0.43 mmHg, respectively, $p > 0.05$), but there was a significant difference in the outflow facility coefficient between the groups before patients received the glyceryl ascorbate test (0.19±0.021 mm^3/min/mmHg and 0.11±0.008 mm^3/min/mmHg, respectively, $p<0.05$). At first sight, it appears that this makes it possible to assess the state of Schlemm's canal without performing a preliminary glyceryl ascorbate test. Detailed analysis of the results of electronic tonography in each patient demonstrated that there is no clear relationship between the baseline outflow facility coefficient and the response of ocular drainage system to the test. We believe this aspect of the state of hydrodynamics in the glaucoma eye is promising for further research since, to the best of our knowledge, no study has reported on this subject.

Conclusion

The current study demonstrated that the success rate of SLT in eyes with POAG was 69.2%. The success rate, however, may reach 100% if SLT is performed only in POAG eyes with a functional blockage of SC. In POAG eyes with a functional blockage of SC, SLT resulted in a 25.18 percent IOP reduction, 40 percent increase in the outflow facility coefficient, and 46.63 percent decrease in the Becker's coefficient, thus indicating normalization of ocular hydrodynamics. If established, the functional state of SC may be used for determining indications and contraindications for SLT in POAG in an effort to optimize treatment outcomes.

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Disclosures

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Author's contribution: *All authors analyzed the results and approved the final version of the manuscript.*

Ethical considerations: This study was approved by the local bioethics committee and adhered to the Declaration of Helsinki, European Convention on Human Rights and Biomedicine, and relevant laws of Ukraine. Appropriate informed consent was obtained from patients. Animals were not used in this study.

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Abbreviations: ACA, anterior chamber angle; BK, Becker’s coefficient; C, outflow facility coefficient (a coefficient representing the outflow in cubic millimeters per minute per millimeter of mercury pressure gradient); F, aqueous outflow per minute; IOP, intraocular pressure; P0, true intraocular pressure; POAG, primary open-angle glaucoma; SC, Schlemm’s canal; SLT, selective laser trabeculoplasty