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SALT Trial: Steroids after Laser Trabeculoplasty

Impact of Short-Term Anti-inflammatory Treatment on Selective Laser Trabeculoplasty Efficacy

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Purpose: This study examined whether short-term use of topical nonsteroidal anti-inflammatory drug (NSAID) or steroid therapy affected the efficacy of selective laser trabeculoplasty (SLT).

Design: Double-masked, randomized, placebo-controlled, dual-center, multisurgeon trial.

Participants: Patients older than 18 years with intraocular pressure (IOP) of more than 18 mmHg for whom the clinician decided SLT was the appropriately indicated therapy were randomized to 1 of 3 groups in a ratio of 1:1:1 as follows: ketorolac 0.5%, prednisolone 1%, or saline tears.

Methods: After SLT, patients randomized into each group were instructed to use an unmarked drop 4 times daily starting the day of SLT and continuing for 4 additional days. The Kruskal-Wallis test and Wilcoxon rank-sum test were used for continuous variables when comparing 2 or 3 treatment groups, respectively. The Fisher exact test was used for categorical variables.

Main Outcome Measures: The primary outcome of this study was IOP at 12 weeks. Secondary outcome measures included IOP at 1 and 6 weeks, patient-reported pain, and detectable anterior chamber inflammation.

Results: Ninety-six eyes of 85 patients fit inclusion criteria and were enrolled between the 2 sites. The NSAID, steroid, and placebo groups were similar in baseline demographics and baseline IOP (mean, 23.3±3.9 mmHg; $P = 0.57$). There was no statistically significant difference in IOP decrease among groups at week 6. Both the NSAID and steroid groups showed a statistically significantly greater decrease in IOP at week 12 compared with the placebo group (mean, −6.2±3.1 mmHg, −5.2±2.7 mmHg, and −3±4.3 mmHg, respectively; $P = 0.02$ [analysis of variance] and $P = 0.002$ [*t* test] for NSAID vs. placebo groups; $P = 0.02$ for steroid vs. placebo groups).

Conclusions: Significantly better IOP reduction at 12 weeks was measured in eyes treated with steroid or NSAID drops after SLT. Short-term postoperative use of NSAID or steroid drops may improve IOP reduction after SLT. Longer-term follow-up studies are indicated. *Ophthalmology 2019;126:1511-1516 Published by Elsevier on behalf of the American Academy of Ophthalmology*

Laser trabeculoplasty is a frequently used glaucoma therapy that is relatively safe and effective in lowering intraocular pressure (IOP). Argon laser trabeculoplasty (ALT) was identified first as a means of lowering IOP,[1] and subsequent studies demonstrated that ALT was a safe and effective means of lowering IOP in patients with primary open-angle glaucoma (POAG) as well as certain forms of secondary open-angle glaucoma (OAG) such as pigmentary glaucoma and pseudoexfoliation glaucoma syndromes.[2,3] Subsequently, selective laser trabeculoplasty (SLT) was described as an alternative method of lowering IOP in patients with OAG.[4] Selective laser trabeculoplasty uses a neodymium:yttrium−aluminum−garnet laser that selectively targets pigmented trabecular meshwork cells and uses very short pulses of low energy to stimulate the cells. The mechanism of action of these lasers is not completely understood and is likely different between ALT and SLT, but several current theories for SLT mechanism of action are discussed below.

There is typically a short-term anterior chamber inflammatory response that may follow ALT or SLT, and dating back to the initial experience with ALT, surgeons routinely prescribe short-term anti-inflammatory drugs after laser treatment, especially steroids. The Fluorometholone-Laser Trabeculoplasty Study Group suggest that use of fluorometholone is effective in attenuating inflammation and has no clinically significant impact on the outcome of ALT or on the incidence of IOP spikes during the immediate period after ALT.[5] Studies that used nonsteroidal anti-inflammatory drugs (NSAIDs) after ALT suggest that the use of NSAIDs represents a very efficient anti-inflammatory therapy after ALT,[6,7] suggesting that the postoperative steroids could be replaced with NSAIDs. Clinical trials of SLT efficacy also use these

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medications for 4 to 7 days after laser treatment.[8–17] However, as discussed below, it has been hypothesized that inflammatory signaling response may promote SLT efficacy,[18] raising the question of whether such steroid or NSAID use may actually inhibit SLT's IOP-lowering effect. In this study, we examined whether short-term use of steroids or NSAIDs affect the efficacy of SLT to 12 weeks.

Methods

This double-masked, randomized, placebo-controlled clinical trial was conducted at the Bascom Palmer Eye Institute in Miami, Florida, and the Eye Center of the University of Pittsburgh Medical Center in Pittsburgh, Pennsylvania, and adhered to the tenets of the Declaration of Helsinki. Patients provided written informed consent before participating in the study. The study was approved by the institutional review boards of the participating institutions. The trial design and outcomes were registered on Clinicaltrials.gov (identifier, NCT00981435). Patients were enrolled from September 2009 through August 2013.

Inclusion criteria were patients older than 18 years with IOP of more than 18 mmHg before SLT for whom the clinician decided SLT was the appropriately indicated therapy. Patients must have been diagnosed with ocular hypertension, defined as IOP of more than 21 mmHg, but without visual field deficits, or OAG, including POAG, pseudoexfoliation glaucoma, or pigmentary glaucoma. Exclusion criteria were patients with traumatic (angle-recession), congenital, juvenile-onset, or combined-mechanism glaucomas; patients who had undergone previous incisional or ablative glaucoma surgery; and patients who had undergone previous ALT, SLT, iridoplasty, or peripheral iridotomy. Also excluded were patients with corneal edema out of concern that applanation would be inaccurate or the trabecular meshwork would not be visible adequately for gonioscopy; patients taking systemic or ocular steroids for any reason; known steroid responders; patients with a history of uveitis in either eye; or patients who were pregnant or within 3 months of giving birth. Both eyes from the same patient could be included in the study if both eyes met the inclusion and exclusion criteria, but in such cases, the 2 eyes were enrolled serially and were randomized separately.

For patients who met study criteria and consented to participation, baseline ocular assessment included best-corrected visual acuity, slit-lamp assessment of the anterior segment of the eye, and gonioscopy of the angle. Trabecular meshwork pigmentation was graded according to a standard scale where 0 is no pigment and 4+ is dense homogeneous pigment (originated by Coherent Medical, Santa Clara, CA). Intraocular pressure was measured with Goldmann applanation with at least 2 recordings from 2 different visit days before patients were enrolled in the study and on the operative day before the procedure. Stereoscopic optic nerve examination was performed with a 90-diopter lens.

For SLT, all patients without medical contraindications were pretreated with 1 drop of apraclonidine immediately before the laser treatment to prevent a postoperative IOP spike (defined as a rise in IOP of >6 mmHg 1 hour after laser treatment). One hundred eighty degrees to 360° of the angle were treated with SLT according to the surgeon's discretion using 50 to 100 nonoverlapping applications, with a spot size of 400 μm centered on the trabecular meshwork and pulse duration of 3 ns. The initial energy used was 0.8 mJ and the energy was titrated to so-called champagne bubble formation. One hour after treatment, the IOP was checked, and anterior chamber cells and flare were each graded on a scale of 0 to 4+.

Block randomization was generated with a random number generator in Microsoft Excel (Microsoft, Redmond, WA) with a block size of 30. Random number generation between 0 and 0.33, between 0.33 and 0.66, and between 0.66 and 1 were assigned to the 3 arms by an unmasked study coordinator (M.N.). The output block randomization was hidden from the physicians who were masked to the random allocation sequence and to the assignment of study participants to treatment arms. Patients were randomized to 1 of 3 groups: ketorolac 0.5% (NSAID), prednisolone acetate 1% (steroid), or saline tears (placebo). The bottles were labeled with patient name, study participant number, and dosing instructions only. All groups used their study drop 4 times daily for 5 days, where the first day was the day of SLT. Patients were advised to continue the same glaucoma medications as before the laser treatment, to the extent that the treating physician did not find such a regimen medically contraindicated.

On postoperative day 1 and again between postoperative days 5 and 7, patients were examined for anterior chamber cells and flare by the masked physician (E.A., N.L., J.S.S., or J.L.G.) and IOP was measured using Goldmann applanation tonometry by a masked technician. Per protocol, in patients found to have an IOP rise of more than 5 mmHg, the treating physician was free to add antihypertensive medication, but a rise of more than 5 mmHg was never detected. During postoperative weeks 6 and 12, best-corrected visual acuity and IOP were measured by a masked technician, eyes were examined by the masked physician for anterior chamber reaction, and gonioscopy was carried out to look for the presence of peripheral anterior synechiae.

Outcomes and Statistical Methods

The primary outcome of this study was the effect of short-term NSAID and steroid use on the IOP-lowering effect of SLT compared with placebo at 12 weeks measured as longitudinal change from baseline, as prespecified in a statistical analysis plan and noted on clinicaltrials.gov. A power analysis performed before trial initiation for this primary end point of IOP change at 12 weeks showed that to detect a difference in IOP change

Table 1. Demographics of Patients

	Total	NSAID	Steroid	Saline Tears
Patient eyes, no.	96	28	37	31
Gender				
Female	55 (57)	13 (46)	23 (62)	19 (61)
Male	41 (43)	15 (54)	14 (38)	12 (39)
Ethnicity, no. (%)				
White	52 (54)	17 (61)	20 (54)	15 (48)
Hispanic	23 (24)	4 (14)	9 (24)	10 (32)
Black	21 (22)	7 (25)	8 (22)	6 (20)
Diagnosis, no. (%)				
POAG	73 (75)	20 (71)	28 (76)	24 (78)
PXG	4 (4)	0 (0)	3 (8)	1 (3)
OHT	20 (21)	8 (29)	6 (16)	6 (19)
Eye, no. (%)				
Right	55 (57)	18 (66)	20 (54)	17 (55)
Left	41 (43)	10 (34)	17 (46)	14 (45)
Cup-to-disc ratio				
Mean	0.64	0.64	0.63	0.65
Minimum	0.1	0.1	0.15	0.3
Maximum	0.99	0.9	0.95	0.99
Degrees of SLT treatment, no. (%)				
180	34 (36)	7 (25)	14 (37)	14 (45)
270	11 (12)	4 (14)	5 (14)	2 (6.5)
360	50 (52)	17 (61)	18 (50)	15 (48)

NSAID = nonsteroidal anti-inflammatory drug; OHT = ocular hypertension; POAG = primary open-angle glaucoma; PXG = pseudoexfoliation glaucoma; SLT = selective laser trabeculoplasty.

Table 2. Intraocular Pressure Measurements at Each Time Point as Well as the Change in Intraocular Pressure from Baseline at 6 and 12 Weeks

	Total Group	NSAID	Steroid	Saline Tears
Baseline	23.3±3.9 (n = 96)	23.3±4.2 (n = 28)	23.7±4.4 (n = 37)	22.7±7 (n = 31)
6 wks	17.8±3.9 (n = 87)	17.3±4.4 (n = 27)	17.9±3.7 (n = 33)	18.5±3.5 (n = 27)
12 wks	18.2±4 (n = 81)	17.07±4.2 (n = 27)	18.1±3.7 (n = 29)	19.4±4 (n = 25)
Change at 12 wks from baseline	−4.8±3.6	−6.2±3.1	−5.2±2.7	−3±4.3

NSAID = nonsteroidal anti-inflammatory drug.
Data are mean ± standard deviation (mmHg) unless otherwise indicated.

between groups of 4 mmHg, with an α of 90% and a β of 5%, would require 30 eyes per group or at least 90 total eyes. The distribution of baseline characteristics was compared among the NSAID, steroid, and placebo groups, and all outcomes were analyzed on an intention-to-treat basis. The Kruskal-Wallis test and Wilcoxon rank-sum test were used for continuous variables when comparing 3 or 2 treatment groups, respectively. The Fisher exact test was used for categorical variables. Secondary outcomes included IOP change from baseline at 6 weeks and visual acuity, anterior chamber reaction, number of drugs used, and ocular discomfort (pain, itching, burning, foreign body sensation) at any time.

Results

Ninety-six eyes of 85 patients were enrolled between the 2 sites; by eyes, 57% were female and 57% were right eyes. Patients self-identified as white (54%), Hispanic (24%), and black (22%). Mean cup-to-disc ratio was 0.64. Diagnosis by eye was POAG in 75%, pseudoexfoliation glaucoma in 4%, and ocular hypertension in 21%. The SLT treatment was 360° in 52% of the eyes, 270° in 12% of the eyes, and 180° in 36% of the eyes. The NSAID, steroid, and placebo groups were similar, with no statistically significant differences in baseline demographics, including gender, ethnicity, race, current medical ocular hypotensive therapies, cup-to-disc ratio, OAG diagnosis, or eye, nor in degrees of SLT treatment (Table 1). One patient received an additional drop of apraclonidine because of an IOP spike after laser treatment. There were no exclusions after randomization. Eighty percent of the study eyes completed 100% of study visits, and 0% of patients reported not using study drops after SLT as prescribed.

Baseline IOP for the entire group was 23.3±3.9 mmHg, with the baseline IOP between the groups not being significantly different (P = 0.57, analysis of variance; 23.3±4.2 mmHg, 23.7±4.4 mmHg, and 22.7±7 mmHg in the NSAID, steroid, and placebo groups, respectively). Although there was a trend toward a decrease in IOP at 1 week, it was not significant in any of the groups (P = 0.0904). At weeks 6 and 12, SLT treatment showed significant IOP reduction in all groups, with week 6 IOPs of 17.3±4.4 mmHg, 17.9±3.7 mmHg, and 18.5±3.5 mmHg and week 12 IOPs of 17.1±4.2 mmHg, 18.1±3.7 mmHg, and 19.4±4 mmHg in the NSAID, steroid, and placebo groups, respectively (Table 2). At week 6, there was no statistically significant difference in IOP decrease among groups (Fig 1; P = 0.14, analysis of variance), but at the primary end point of change from baseline IOP at week 12, both the NSAID and steroid groups showed a statistically significantly lower IOP at week 12 compared with the saline group, a decrease of −6.2±3.1 mmHg, −5.2±2.7 mmHg, and −3±4.3 mmHg in the NSAID, steroid, and placebo groups, respectively (Fig 2; P = 0.0044 [analysis of variance] and P = 0.002 [post hoc t test] for NSAID vs. placebo groups; P = 0.02 for steroid vs. placebo groups). As a sensitivity analysis, a post hoc multiple linear regression (analysis of covariance) for change in IOP at 12 weeks using baseline IOP as a covariate was performed, and the effect of treatment group remained statistically significant (P = 0.004). The correlation coefficient between baseline IOP and final IOP was 0.59.

Regarding secondary outcomes, anterior chamber reaction was similar and not significantly different among the 3 groups at 1 hour, and there was no detectable anterior chamber reaction in any patients in the 3 groups at week 1, week 6, or week 12 (Table 3). Similarly, at the 1-hour and 1-week time points, patients reporting ocular discomfort (defined as pain, itching, burning, or foreign body sensation) did not differ between groups (Table 4).

Discussion

This study found a statistically significant effect of topical anti-inflammatory medications on the efficacy of SLT, statistically significant at the week 12 primary end point and trending toward this difference at the week 1 and week 6 secondary end points. There was no statistical difference in baseline IOP between groups. Although the slightly lower baseline IOP in the saline group may have penalized analysis of IOP change in this arm slightly, post hoc sensitivity testing confirmed a statistically significant effect of treatment when analyzing baseline IOP as a covariate. Compared with placebo, which did show a significant response to

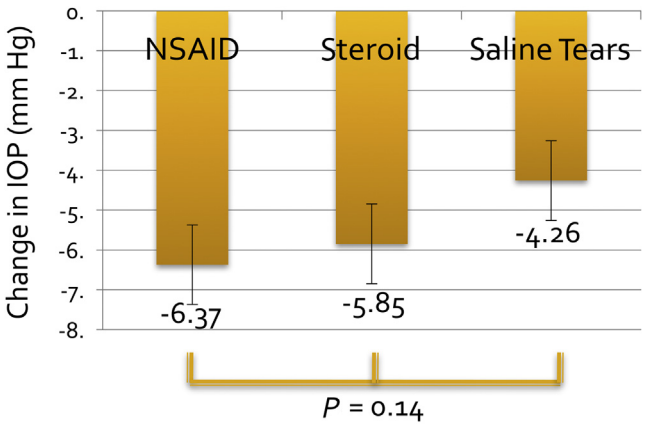

Figure 1. Bar graph showing intraocular pressure (IOP) change from baseline at week 6 (P value represents analysis of variance). NSAID = nonsteroidal anti-inflammatory drug.

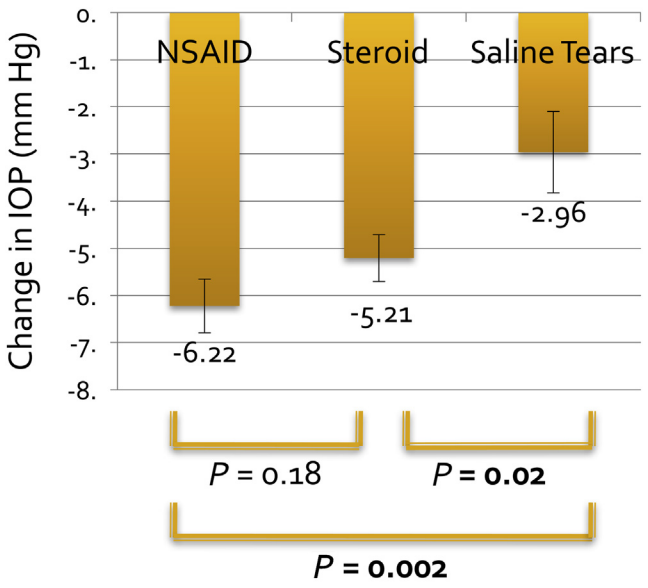

Figure 2. Bar graph showing intraocular pressure (IOP) change from baseline at week 12 (*P* values represent post hoc *t* test after statistically significant analysis of variance). NSAID = nonsteroidal anti-inflammatory drug.

therapy, the steroid group showed a more than 2-mmHg IOP decrease, and the NSAID group showed a more than 3-mmHg IOP decrease, although the difference was not great enough to confer statistical significance between steroid and NSAID treatment.

These data suggest that the medication in the first 5 days after SLT takes weeks to confer an effect on lowering IOP. The mechanism for SLT is not understood completely, but there are a mechanical theory and cellular and molecular biologic theories.[19] Briefly, the mechanical theory suggests thermal energy burns the tissues and causes collagen to shrink and contract, stretching open the uveoscleral

Table 3. Anterior Chamber Reaction of Cell–Flare at Each Interval by Group Based on the Standardization of Uveitis Nomenclature Criteria

	Total	NSAID	Steroid	Saline Tears	*P* Value
1 hr, no. (%)					0.34
0	39 (44.8)	10 (38.5)	11 (35.5)	18 (60.0)	
1+	20 (23.0)	5 (19.2)	10 (32.2)	5 (16.7)	
2+	17 (19.5)	8 (30.8)	6 (19.3)	3 (10.0)	
3+	11 (12.7)	3 (11.5)	4 (12.9)	4 (13.3)	
Week 1, no.					
0	92	26	35	31	—
1–3+	0	0	0	0	
Week 6, no.					
0	84	25	32	27	—
1–3+	0	0	0	0	
Week 12, no.					
0	76	25	27	24	—
1–3+	0	0	0	0	

— = not performed as all eyes recorded as 0; NSAID = nonsteroidal anti-inflammatory drug.

Table 4. Secondary Outcome: Number and (Percentage) of Patients Experiencing Ocular Discomfort Defined as Pain, Itching, Burning, and Foreign Body Sensation

	NSAID	Steroid	Saline Tears
1 hr	2 (7)	5 (14)	8 (26)
1 wk	6 (23)	7 (19)	8 (26)
6 wks	1 (4)	0 (0)	1 (4)
12 wks	1 (4)	0 (0)	0 (0)

NSAID = nonsteroidal anti-inflammatory drug.

trabecular meshwork and Schlemm's canal,[20,21] but this may be less plausible for SLT compared with ALT, given the lack of documentable thermal burns in SLT. More likely, the energy from the laser may stimulate cellular recruitment and remodeling of the extracellular matrix,[22] perhaps through production of enzymatic metalloproteinases,[18,23,24] cell division, trabecular meshwork repopulation, or a combination thereof.[25] It has been hypothesized that activation of inflammatory pathways such as the cytokines interleukin 1b, interleukin 8, and tumor necrosis factor α may be important for eliciting SLT's effect on trabecular meshwork remodeling and IOP reduction,[18] although cellular effects on trabecular meshwork niche stem cells by short-term anti-inflammatory therapies are not yet known. Thus, pharmacologically interfering with molecular pathways, including such cytokines through use of steroids or NSAIDs in the days immediately after the SLT, may block eventual IOP-lowering efficacy. Alternatively, one may hypothesize that steroid or NSAID use may block negative inflammatory pathways such as those associated with fibrosis and scarring, thereby increasing SLT efficacy. Our data suggest that because NSAID or steroid use promoted SLT efficacy, their mechanism of action may be through blocking such negative inflammatory pathways. We did not observe overt inflammation that differed between groups, so resolving the mechanism of action may require other (e.g., laboratory-based) studies.

Several groups have not previously detected any effect of topical anti-inflammatory medications after laser trabeculoplasty. In 25 POAG patients undergoing bilateral 360° SLT and randomized to prednisolone acetate 1% versus placebo 4 times daily in 1 eye for 1 week, there was no significant difference in IOP at 1 week, 1 month, and 3 months. The baseline IOP in this study was lower at 18.4 mmHg.[26] In SLT patients randomized to prednisolone acetate 1%, ketorolac 0.5%, or artificial tears 4 times daily for 5 days, there was no difference in mean change in IOP at 1 month or 1 year,[27] but again in that study, baseline IOP (19.1 mmHg, 19.6 mmHg, and 18.5 mmHg in prednisolone, ketorolac, and artificial tears groups, respectively) was lower than that found in our and other similar studies,[10,28,29] and higher baseline IOP has been associated with a greater absolute decrease in IOP.[30] In a retrospective chart review comparing loteprednol versus no loteprednol for 5 to 7 days after 360° SLT, a trend toward lower IOP was detected in the no loteprednol group, but this was not statistically significant.[31] Most

recently, De Keyser et al[32] randomized patients to dexamethasone or control and indomethacin or control. They found no difference in the rate of inflammation or IOP efficacy at 1-, 3-, or 6-month follow-ups, although again, baseline IOPs were much lower (13−14 mmHg). The larger sample size and higher starting IOPs in our prospective, randomized, double-masked study may explain the difference in this study's ability to detect differences favoring the use of steroid or NSAID after SLT.

Limitations to our study include the intention-to-treat analysis that did not include any check of compliance of eye drop use other than patient report, the relatively short-term follow-up, and the small sample size. Certainly, a larger patient population would be beneficial for follow-up studies. The statistical analysis was carried out using a longitudinal design examining difference in change from baseline IOP, given the number of participants. According to our power calculations based on the primary end point at 12 weeks, more participants would need to be enrolled to implement a longitudinal, nested, mixed-effect model. A more complex model could include a multivariate analysis and could adjust for some participants having both eyes enrolled. A larger study with more broadly recruited diagnoses also would be needed to assess differences in SLT response based on type of glaucoma, and similarly, patients in this study were not stratified according to use of medication before SLT. Although the groups were not statistically different regarding preoperative medication, a study design or even a post hoc analysis of which medications were used would require much larger patient cohorts to examine different classes of concomitant topical medication comprehensively.

This study also allowed variable degrees of SLT treatment according to the treating clinician's preference. Degree of treatment may have been influenced a priori by severity of a given patient's disease or intraprocedurally by apparent laser uptake efficacy, trabecular meshwork pigmentation, or other factors. Values for total energy applied between groups were not recorded as study parameters, but the randomization kept the treating clinician completely masked, and as a surrogate, the variation in treatment extent recorded as angle degrees treated was found to be similar in each group, so we do not hypothesize that total laser energy interacts with topical therapy in determining IOP outcome. Future studies could be designed to determine if other, more potent NSAIDs produce comparable benefit.

In conclusion, this double-masked placebo-controlled study showed statistically significantly better IOP reduction at 12 weeks in eyes treated with steroid or NSAID drops than was seen in a placebo-controlled group after SLT. Short-term postoperative use of NSAID or steroid drops may improve efficacy of IOP reduction after SLT, but additional long-term outcome studies are reasonable when considering whether to change clinical practice.

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Abbreviations and Acronyms:
ALT = argon laser trabeculoplasty; **IOP** = intraocular pressure; **NSAID** = nonsteroidal anti-inflammatory drug; **OAG** = open-angle glaucoma; **POAG** = primary open-angle glaucoma; **SLT** = selective laser trabeculoplasty.

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