Comparison of successful outcome predictors for MicroPulse® laser trabeculoplasty and selective laser trabeculoplasty at 6 months

Matthew T Hirabayashi1
Trevor L Rosenlof1,2
Jella A An1,2

1University of Missouri Columbia School of Medicine, Columbia, MO, USA; 2Mason Eye Institute, Department of Ophthalmology, University of Missouri, Columbia, MO, USA

Purpose: To identify and compare factors predictive of successful outcome for MicroPulse® laser trabeculoplasty (MLT) and selective laser trabeculoplasty (SLT).

Methods: 50 MLT-treated eyes and 50 SLT-treated eyes of open-angle glaucoma patients were reviewed for baseline characteristics, pre- and postoperative IOP and medications, and adverse events including postoperative IOP elevation >5 mmHg (IOP spikes) through 6 months of follow-up. Success was defined as ≥20% IOP reduction or ≥1 medication reduction without additional IOP lowering procedures at 6 months follow-up.

Results: MLT and SLT had similar success rates (44% vs 40%, P=0.983). Older age predicted success for SLT (P=0.013) but not MLT (P=0.154). Both MLT and SLT led to greater IOP lowering in patients with baseline IOP >18 mmHg, but only for SLT did baseline IOP have a significant association with success (P=0.035 vs P=0.983). Number of laser shots was associated with success in MLT (P=0.031) but not in SLT (P=0.970). Glaucoma severity and pigmentation of the trabecular meshwork (PTM) were not associated with rate of success for either group. The rate of IOP spikes was significantly (P=0.022) higher in the SLT group (10%) compared to none in the MLT group. No other complications or visually significant adverse events occurred in either group.

Conclusion: Although MLT and SLT resulted in similar success rates, older age and higher baseline IOP predicted success for SLT while MLT was equally efficacious regardless of these factors. Glaucoma severity and PTM were not associated with success of either laser procedures. 10% of SLT patients experienced IOP spike post procedure, whereas none in the MLT group did. MLT may be a safer alternative to SLT that is effective in lowering IOP and need for medications for a wider variety of patients with open angle glaucoma.

Keywords: glaucoma, intraocular pressure, ocular hypertension, MLT, SLT, POAG

Introduction

Since the development of argon laser trabeculoplasty (ALT) in the 1970s, the use of laser trabeculoplasty for open-angle glaucoma has played a crucial role in management, ranging from initial to refractory glaucoma treatment.1,2 The current American Academy of Ophthalmology (AAO) guidelines suggest several scenarios in which laser trabeculoplasty is an appropriate first-line therapy, especially in patients at risk for nonadherence or with poor tolerance to ocular hypotensive medication.3 Laser trabeculoplasty has continued to evolve with improving technology. Selective laser trabeculoplasty (SLT) was introduced in 1995 and has proven to be equivalent in terms of efficacy to ALT without structural damage to
the trabecular meshwork (TM) through selective energy delivery to the pigmented trabecular meshwork.4

MicroPulse® laser trabeculoplasty (MLT), the latest laser technology, was introduced in 2008. It delivers under 1% of the energy of ALT and specifically targets the cells of the pigmented TM with the 532 nm near-infrared diode laser.2 This wavelength was the factory setting which is used to target pigmented cells of the TM equivalent to SLT. A parameter called “duty cycle” indicates the percentage of time the laser is active compared to the time the laser is at rest. This pattern of energy delivery offers a proposed advantage over ALT or SLT by allowing tissue cooling in between pulses to minimize unintended structural and collateral tissue damage.2,6 Previous studies have shown that MLT may have superior efficacy and safety to ALT and comparable efficacy to SLT.7–9

Whereas SLT energy is titrated based on visible microbubbles, typically requiring less energy in heavily pigmented TM, it is not customary to deviate from the manufacturer’s recommended energy setting (1,000 mW power, 300 μm spot size, 300 ms duration with 15% duty cycle, 360° treatment) during MLT. Higher rate of sustained IOP elevation in patients with a heavily pigmented TM after SLT has been reported,10 but the efficacy of the procedure has not shown to depend on the pigmentation of the TM (PTM),11 possibly due to the fact that energy settings were not kept constant.

To our knowledge, robust literature that has sought to describe characteristics of good candidates for MLT is lacking. Our primary goal was to identify predictive factors for successful 6 month outcomes of MLT and compare them to those of SLT by correlating demographics and preoperative clinical characteristics of patients to postlaser IOP or medication reduction. Our secondary goal was to compare the rate of IOP and medication reduction and any laser-related adverse events including IOP spikes between MLT and SLT through 6 months follow-up.

Materials and methods
Patient selection and data collection
The University of Missouri Institutional Review Board (IRB) granted a waiver of informed consent due to the retrospective nature of this study and data was de-identified. All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and national research committee and with the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards. A retrospective review of electronic medical records of all consecutive adult patients with open-angle glaucoma who received SLT or MLT between July 2017 and May 2018 at the University of Missouri was performed after obtaining IRB approval (#2011753). All patients seen prior to December 2018 received SLT and MLT was used exclusively afterwards. The inclusion criteria were patients with a diagnosis of primary or secondary open-angle glaucoma per ICD-10 guidelines12,13 at the time of laser trabeculoplasty, 360-degree treatment per session, and a minimum 6 months of follow-up after laser treatment. Patients who received SLT over 180° of the TM were excluded from the study. All patients who required repeat treatment or additional IOP-lowering procedure were included and considered failure of treatment.

A total of 50 eyes of 48 patients who received MLT and 50 eyes from 42 patients who received SLT were identified and included in the study. Each eye was considered independently. We recorded age, gender, ethnicity, glaucoma type, glaucoma severity, PTM, IOP and the number of medications as baseline characteristics. For outcome measures, we recorded IOP, number of medications and any adverse events at each postoperative visit at 1 hour, 2 weeks, 2 months and 6 months after laser treatment. Adverse events included IOP spike (defined as postoperative elevation of IOP ≥5 mmHg from baseline), and any vision loss ≥2 Snellen lines during the follow-up period.

Glaucoma was diagnosed using visual field testing and assessment of the optic nerve and retinal nerve fiber layer using slit lamp ophthalmoscopy and optical coherence tomography (OCT). Glaucoma severity was defined by ICD-10.13,14

Laser techniques and postoperative protocols
All MLT was performed with IQ 532™ laser (Iridex Corporation, Mountain View, CA, USA) with 532 nm wavelength, 15% duty cycle (500 Hz), duration of 300 ms, spot size 300 micrometer and 1,000 mW of power over 360° of angle per procedure. The SLT was performed with 532 nm frequency doubled Q-switched Nd:YAG laser with fixed 3 ns pulse and 400 micrometer spot size, and variable power between 0.6 and 1.4 mJ, titrated to visible microbubble, over 360° of angle per procedure. No additional ocular hypotensive medication was given at the time
of laser, unless IOP spike was noted at 1 hour post laser. IOP was checked with a Goldmann applanation tonometer by a skilled technician or the treating physician prior to laser, as well as at 1 hour, 2 weeks, 2 months and 6 months after laser. Visual acuity, slit lamp examination and gonioscopy was performed at 2 weeks, 2 months and 6 months follow-up. All patients were kept under the same medications until seen 2 months postoperatively, when they were adjusted at the surgeon’s discretion based on the target IOP and sign of progression.

Outcome measures
For the primary outcome, we defined success as reduction of ≥20% IOP or ≥1 glaucoma medication without requiring additional IOP lowering procedures at 6 months, and sought for possible correlation with patient age, severity of the glaucoma, PTM, total number of laser shots applied per session, and baseline IOP as possible predictive factors. Any need for additional IOP lowering procedure, including repeat laser trabeculoplasty, within 6 months of follow-up was considered treatment failure. Patients with adverse events or IOP spikes were still considered success as long as they met the success criteria. For secondary outcome, we compared mean and percentage IOP and medication reduction as well as any laser-related adverse events between the two groups.

Statistical analysis
Baseline characteristics and IOP/medication reduction between MLT and SLT were compared using chi-square, Fisher’s exact, Student’s t-test, and Mann–Whitney U test. Rates of success and IOP spikes were compared with chi-square and Fisher’s exact tests. Preoperative vs postoperative IOP and medication number for each procedure were compared with paired t-tests and Wilcoxon Rank-Sign test.

To determine if glaucoma severity, PTM, and number of laser shots predicted success, a logistic regression was performed with success as a dichotomous outcome. For age and preoperative IOP, ANOVA-type model was used for comparisons. For both tests, a random effect for the patient was used for comparisons to account for those who contributed two eyes.

Central tendency for normally distributed data is presented as mean ±SD and central tendency for non-normally distributed data is presented as mean ±SD (median IQR) unless otherwise specified. We used SPSS version 24.0 (IBM Corporation, Armonk, NY, USA) for all statistical analysis.

Results
Preoperative characteristics
Table 1 summarizes and compares the preoperative characteristics and the number of laser shots of patients who had MLT or SLT. The only significant difference between the groups was mean number of laser shots which was higher in the MLT group, likely due to smaller spot size. Patient age, gender, ethnicity, glaucoma type and severity, baseline IOP and number of medications were not significantly different between the two groups.

Predictive factors for success
We report our findings for predictive factors for success for both MLT and SLT in Table 2 and discuss them individually below.

Age
The age of patients receiving MLT ranged from 45–91 years old. The mean age of successful cases was 70.2 ±11.7 years, while that of unsuccessful cases was 65.9 ±8.0 years. Patient age did not significantly predict success of MLT at 6 months (P=0.154).

For SLT, age ranged from 47–96 years old. The mean age of successful cases was 73.7±11.8 years and that of unsuccessful cases was 65.9±9.1 years. For SLT, older age was significantly associated with success (P=0.013).

Severity of glaucoma
Glaucoma severity was categorized into mild, moderate, and severe based on visual field defect according to the current ICD-10 guidelines.12,13 Severity of glaucoma did not appear to significantly predict successful outcome for either MLT (P=0.585) or SLT (P=0.583).

TM pigmentation
Degree of PTM was categorized into “light” (trace to 2+) or “heavy” (3–4+), as graded by the primary surgeon at the time of the laser treatment. For MLT, 48.7% (19/39) of light TM eyes were successful compared to 27.3% (3/11) of heavy TM eyes. For SLT, 45.0% (18/39) of light TM eyes were successful compared to 20.0% (2/10) of heavy TM eyes. There was no statistically significant association between degree of PTM and success rate for either MLT (P=0.305) or SLT (P=0.149).
The total number of laser shots delivered to the pigmented TM over 360 degree at initial procedure ranged from 86–192 for MLT and 44–139 for SLT. For MLT, successful cases had a mean of 122.6±20.8 total shots compared to 136±27.16 shots in unsuccessful cases. Fewer number of shots were associated with success (P=0.031) in MLT. For SLT, successful cases had a mean of 84.9±17.4 compared to 84.5±20.6 shots in unsuccessful cases. Shot number did not significantly predict success in SLT group (P=0.970).

Baseline IOP
For MLT, mean baseline IOP for successful cases was 19.0 ±3.1 mmHg compared to 18.5±3.9 mmHg for unsuccessful cases. Baseline IOP was not a statistically significant predictor for success (P=0.983). For SLT, mean baseline IOP for successful cases was 19.8±3.8 mmHg compared to 16.9±5.2 mmHg for unsuccessful cases. Baseline IOP significantly predicted SLT success at 6 months (P=0.035).

We also divided patients for both procedures into baseline IOP ≤18 mmHg and >18 mmHg (Table 3). For MLT, IOP reduction in patients with baseline IOP ≤18 mmHg was 0.9±3.4 mmHg compared to 3.4±4.3 mmHg in those with baseline IOP >18 mmHg (Figure 1). This difference in IOP reduction was not statistically significant (P=0.053). For SLT, IOP reduction in patients with baseline IOP ≤18 mmHg was −0.6±3.6 mmHg compared to 5.2 ±8.3 mmHg in those with baseline IOP >18 mmHg. This difference in IOP reduction was statistically significant (P<0.002). The mean IOP reduction for patients with baseline IOP ≤18 mmHg was not significantly different between MLT and SLT (P=0.131). Similarly, mean IOP reduction for patients with baseline IOP >18 mmHg was comparable between MLT and SLT groups (P=0.358).

We considered baseline IOP for medication reduction as well. For MLT, mean ±SD (median [IQR]) medication reduction in patients with baseline IOP ≤18 mmHg was 0.0±1.0 (0[0.0]) compared to 0.3±1.4 (0[1.0]) in those with baseline IOP >18 mmHg. This difference was not

Table 1 Baseline demographic and glaucoma status data

<table>
<thead>
<tr>
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<th>MLT (N=50)</th>
<th>SLT (N=50)</th>
<th>P-value</th>
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<td>Age (years), mean ±SD</td>
<td>67.8±9.9</td>
<td>69.0±10.8</td>
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<td>Gender, N (%)</td>
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<td>33 (66)</td>
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<tr>
<td>Male</td>
<td>17 (34)</td>
<td>24 (48)</td>
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<tr>
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<td>47 (94)</td>
<td>0.271</td>
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<tr>
<td>Other</td>
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<td>3 (6)</td>
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<tr>
<td>Glaucoma type, N (%)</td>
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<tr>
<td>Primary open angle</td>
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</tr>
<tr>
<td>Secondary open angle</td>
<td>9 (18)</td>
<td>3 (6)</td>
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<td>Severity, N (%)</td>
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<tr>
<td>Mild</td>
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<tr>
<td>Moderate</td>
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<tr>
<td>Severe</td>
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<td>20 (40)</td>
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<td>TM pigmentation</td>
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<tr>
<td>Heavy</td>
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<td>Number of laser shots, mean ±SD</td>
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<td>84.6±19.2</td>
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<td>Baseline IOP (mmHg), mean ±SD</td>
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<td>Baseline medications, mean ±SD</td>
<td>2.52±1.31</td>
<td>2.13±1.30</td>
<td>0.893</td>
</tr>
</tbody>
</table>

Notes: Calculated by chi-square, Fisher’s exact, Student’s t-test, and Mann–Whitney U. *Significant difference between both groups at an α of 0.05.
Abbreviations: MLT, MicroPulse® laser trabeculoplasty; SLT, selective laser trabeculoplasty. Other ethnicities, Black and Hispanic; Secondary open-angle, traumatic, pseudoexfoliative and pigment dispersion; TM, trabecular meshwork.
statistically significant (P=0.356). For SLT, IOP reduction in patients with baseline IOP ≤18 mmHg was 0.2±0.9 (0 [0.5]) compared to −0.3±1.1 (0[1.0]) in those with baseline IOP >18 mmHg. This difference in medication reduction was also not statistically significant (P=0.075). The mean medication reduction for patients with baseline IOP ≤18 mmHg was not significantly different between MLT and SLT (P=0.688). Similarly, mean medication reduction for patients with baseline IOP >18 mmHg was comparable between MLT and SLT groups (P=0.859).

Overall success and IOP/medication reduction between MLT and SLT

Table 4 summarizes success and mean reduction of IOP and medication for the MLT and SLT groups. Overall, 44% (22/50) of MLT cases were successful compared to 40% (20/50) of SLT cases. This difference was not statistically significant (P=0.983). MLT group achieved a mean IOP reduction of 2.1±4.1 mmHg (11.5%) to 6-month IOP of 16.5±4.3, compared to 1.8±6.6 mmHg (10.4%) to 6-month IOP of 16.2±6.7

Table 2 Predictive factors for MLT (N=50) and SLT (N=50) success at 6 months

Table 3 IOP reduction at 6 months based on preoperative IOP level for MLT (N=50) and SLT (N=50)
This difference was not statistically significant ($P=0.773$). Mean (median [IQR]) medication reduction was $0.14±1.2$ (0[1]) for MLT group and $0.0±1.0$ (0[0]) for SLT group. Medication reduction was not significantly different between the groups ($P=0.418$).

Complications
None of the patients who received MLT had any reported complications, whereas 10% (5/50) patients who received SLT experienced 1 hour postoperative IOP spikes of $≥5$ mmHg compared to their baseline. The difference in IOP spike rate was statistically significant between the groups ($P=0.022$). There were no other causes of vision loss or need for further procedures, including repeat laser, during the 6-month follow-up period.

Discussion
Although possible predictive factors of SLT outcome have been reported, the literature is generally inconsistent. Many studies, like ours, agree that higher baseline IOP is associated with more successful outcomes$^{15-21}$ and older age as a favorable predictive factor has also been reported.$^{16}$ Others studies reported age as well as PTM or type of glaucoma playing no role in outcomes of laser trabeculoplasty.$^{17,20-23}$ This may be due to different response to laser in different patient populations. For example, our study population was predominantly Midwestern Caucasian with primary open angle glaucoma. Some studies involved only Chinese$^{18,24}$ populations and some occurred in patients with higher rates (73%) of pseudoexfoliation glaucoma (PXG).$^{16}$ Other reasons for the discrepancies in this topic include varying definitions of success, different clinical protocols, study power, and surgeon settings preference. The recently published large-scale randomized controlled trial of SLT vs eye drops for first-line treatment of glaucoma and ocular hypertension patients (LiGHT trial) showed that three-quarters of treatment-naïve patients who received SLT as a primary treatment achieved their severity-based target IOP while being drop-free within the first 3 years of trial, and only six IOP spikes were reported out of over 700 patients.$^{25}$ This demonstration of superior response to SLT may be explained by how different patient populations have varied success to SLT. We suspect that treatment-naïve patients, regardless of degree of visual field defect (determining “severity”), theoretically have the best chance at improving their conventional outflow pathway due to intact function and...
capacity of the TM and distal pathway outflow. Long-term treatment with chronic aqueous suppressants use may lead to decreased function and eventual atrophy of conventional outflow pathways.

Currently, sparse data exists on MLT, especially in comparison to that of SLT. A recent report by Abramowitz et al demonstrated that 26.9% of MLT and 36.0% of SLT patients reached a similar definition of success in the 2–4 year range which is similar to our success rate for both procedures around 40%. Previous studies have reinforced the safety of MLT, but to our knowledge, there is no literature that compared predictive factors of efficacy and safety in MLT in comparison to SLT. Out of all possible baseline characteristics we had considered, as outlined in Table 2, the only association we found for successful outcome of MLT was fewer number of laser shots. Interestingly, the severity of glaucoma and PTM did not predict successful outcome in either group. Regarding the association between fewer laser shots and success in MLT, it is possible that there is a point of diminishing returns in the number of total energy required for laser trabeculoplasty to effectively lower IOP. It is also important to consider that there may have been a selection bias that affected this outcome (surgeons may have treated patients with worse prognosis with more number of shots per session).

Overall success rates for both MLT and SLT at 6 months was near 40% and comparable in both groups. Although both MLT and SLT lead to more IOP reduction in those with higher baseline IOP, the effect of baseline IOP to successful outcome was more strongly correlated in the SLT group. Unlike SLT, MLT also showed comparable efficacy regardless of age of patients. In neither group did medication reduction appear to have an association with baseline IOP, which may be reflected by our conservative treatment protocol, where all patients were kept in the same medications for minimum 2 months, and medication was discontinued one at a time only when IOP reached target.

Although laser-related complications were rare and no loss of vision more than 2 lines was reported in either group at any time point, 10% (5/50) of patients in the SLT group experienced 1 hour postoperative IOP spike (>5 mmHg) while it was absent in the MLT group. Similar findings have been reported in prior studies, particularly Lai et al also finding a rate of 10% using the same definition of IOP spike. While the limited number of spikes makes meaningful statistical analysis impossible, there did not seem to be an association between PTM and IOP spikes. Among 10 patients who had IOP spike, only 2 had heavy PTM. This result was also seen in our study of analyzing nearly 300 patients who received SLT, where there was no association between PTM and IOP spike. However, it has been reported that some secondary glaucoma with heavier PTM, such as pigment dispersion glaucoma and PXG, have higher rate of IOP spike. In our study, although only 2 out of 10 eyes that had IOP spike belonged to patients with PXG, relative incidence of IOP spike among PXG patient was higher (100% PXG) than that of primary open angle glaucoma (POAG) (14.9% POAG). This may suggest that different subtypes of open angle glaucoma may respond differently to SLT regardless of TM pigmentation level. The majority of spikes (7/10) were in eyes with POAG compared to eyes with PXG (2/10) or NTG (1/10) but the vast majority of cases were POAG. The higher IOP spike rate in SLT group of our patient population suggests that closer monitoring of IOP may be warranted post SLT compared to MLT, and MLT may be beneficial in patients with higher baseline IOP on maximal tolerated medications. In treatment-naïve eyes however, this IOP spike rate may be considerably lower, as the LiGHT trial has demonstrated. Similar to LiGHT trial, IOP check at 2 weeks after either SLT or MLT treatment did not change treatment decisions in any of our patients and, therefore, could be eliminated.

In this study, we used 532 nm which was recommended by the company for use of laser trabeculoplasty (IQ 532™, IRIDEX Corporation). This is given the fact that it is equivalent to that of SLT, and it is highly absorbed by melanin in trabecular meshwork. IQ 577™ with 577 nm (yellow) wavelength is preferred as a macular focal laser for retinal disease. The theoretical advantage of using 577 nm for macular treatment (vs 532 nm) is the fact that there is negligible absorption by macular xanthophyll and higher transmission through dense ocular media, while still targeting melanin in retinal pigment epithelium (RPE), enabling observation of tissue reactions at the level of RPE with lower power required. Diode laser with 810 nm wavelength is ideal for transscleral cyclococagulation as it can penetrate deeper into the tissue.

In a randomized prospective trial of 26 POAG patients comparing MLT using a diode laser (810 nm) vs ALT, the MLT group had significantly less IOP reduction compared to
the ALT group, though there was less inflammation in the MLT group. In another prospective cohort study, 577 nm MLT showed a superior result at 6 months. This may demonstrate using a laser with shorter wavelength closer to SLT (532 nm) for laser trabeculoplasty may result in a better IOP reduction.

Lack of statistical association should not be interpreted as lack of correlation, but may be a result of limited sample size and limited variability in some of the categories. For example, the limited variability of types of glaucoma made it impossible to perform a meaningful statistical analysis on this baseline characteristic. However, this level of homogeneity was helpful in evaluating other possible predictive factors such as age, baseline IOP and number of laser shots and PTM as different types of glaucoma did not confound the result. It is to be noted that selection bias did not play a role in patient selection for which laser to perform, as all patients seen prior to December 2017 were treated with SLT, and those seen afterwards were treated exclusively with MLT in our center.

Despite these limitations, the rate of success and failure for SLT was consistent with what had been reported in existing literature. Reported success rates vary between 16 and 66% with higher rates of success in secondary glaucoma. Additional studies with larger patient numbers and prospective randomized controlled trials with longer follow-ups and medication wash-out protocol will be helpful in further exploring comparative long-term outcomes of MLT compared to SLT.

Conclusion
Overall, MLT and SLT had similar 6-month success rates, but IOP spike was only seen after SLT. Older age and higher baseline IOP predicted success for SLT but MLT was equally efficacious regardless of these factors. No preoperative characteristic reliably predicted success of MLT.

Précis
MLT had equal efficacy regardless of patient age and baseline IOP while these factors predicted successful outcome for SLT. Glaucoma severity and TM pigmentation did not correlate with success of either trabeculoplasties.

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