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A Proposal for the Use of a Fixed Low-Energy Selective Laser Trabeculoplasty for Open Angle Glaucoma

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Abstract: Selective laser trabeculoplasty (SLT) has been in routine clinical use for over 20 years with millions of patients successfully treated and a low rate of clinically significant complications. The procedure requires the clinician to manually position the laser beam on the trabecular meshwork using a gonioscopy lens and to titrate the SLT laser energy based on the amount of pigmentation in the angle, as well as the observation of small bubbles produced by the laser effect. We propose that SLT energy titration is unnecessary either to achieve intraocular pressure (IOP) reduction or to minimize potential side effects. Ample evidence to support our proposal includes multiple clinical reports demonstrating comparable levels of IOP reduction resulting from different laser energies, a large variety of energy and other laser parameters used in commercially available SLT lasers, and the nature of the laser-induced changes in the trabecular meshwork tissue with respect to energy. Despite these variations in laser parameters, SLT consistently reduces IOP with a low complication rate. We propose that using low fixed energy for all patients will effectively and safely lower patients' IOP while reducing the complexity of the SLT procedure, potentially making SLT accessible to more patients.

Key Words: selective laser trabeculoplasty, fixed-dose, glaucoma, low-energy beam

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Selective laser trabeculoplasty (SLT) was cleared for commercial use by the FDA in 2001.[1] In the 2 decades that followed, it is likely that millions of patients have been treated with SLT. In 2012, there were 142,682 patients treated with laser trabeculoplasty (assumed to be mainly SLT) in the United States through the federal Medicare service,[2] and from 2019 to 2020, ~11,000 SLT treatments were provided by the UK Hospital Service.[3] In view of the LiGHT study, in which SLT was shown to be superior to glaucoma drugs for initial therapy, it is expected that utilization of SLT will increase.[4–6]

Although SLT is considered to be generally safe, acute postoperative side effects are common. Side effects include transient inflammation of the anterior chamber (30%–80% of patients)[7] and intraocular pressure (IOP) spikes (in up to 26% of patients).[8] Spikes in IOP almost always resolve with no clinical significance with very few cases requiring further treatment, particularly among patients with pigment dispersion.[4,7,9]

Corneal complications of SLT with the potential for vision loss are very rare (often reported individually in case studies),[8] including small reductions in endothelial cell density, short-term corneal edema (in up to 0.8% of treated eyes)[10] uncommonly accompanied by degraded vision, keratitis, and corneal thinning with permanent hyperopia shifts of up to 6D.[7] Permanent corneal endothelial cell failure and corneal edema have been reported in a total of nine cases through 2015.[9]

It is hypothesized that there may be a relationship between the energy dose used and side effects.[7,11] Using lower energies may decrease cumulative tissue damage, which may allow for safer repeat treatments, such as those under investigation in a large trial studying the efficacy of annual re-treatment.[7] A recent SLT review has shown no relation between energy and IOP pressure reduction (IOP energy dose-response), with effectiveness demonstrated even at the lowest energies used (0.2–0.3 mJ/pulse).[12] Low pulse energies may be desirable, which is a significant study objective of the ongoing COAST trial.[7]

A single low SLT energy for all study patients has been reported in work by Gandolfi and Ungaro[13] (360 degrees application of 0.4 mJ, 50–60 spots), Jian et al[14] (360 degrees application of 0.6 mJ, 100 spots), and Xu et al[15] (360 degrees application of 0.3 mJ, 87–120 spots in Chinese patients) with all study results reporting typical SLT IOP reductions. In Xu et al's[15] work, the impetus for a single energy was to make for a more straightforward procedure with no energy adjustments to the bubble threshold. One of us (L.J.K.) has adopted fixed pulse energy for all treated patients, originally 0.6 mJ as Jian et al[14] and then later reduced to 0.4 mJ as Gandolfi and Ungaro,[13] with comparable IOP reduction.

In this article, we provide a justification for using a fixed low-energy laser pulse for all patients. The article will review energy titration, discuss the energy that actually reaches the trabecular meshwork (TM), discuss changes in limbus morphology with pulse energy, and conclude with the variety of laser parameters in commercial SLT lasers. Given the parameter variation in the laser beam and energy that actually reaches the TM, resulting in an effective IOP reduction, as well as the apparent robustness of the resultant IOP reduction across the variation of these parameters, we conclude that using a fixed low-energy pulse seems to be a safe and effective for lowering IOP allowing for a more straightforward SLT procedure with potentially even fewer and less pronounced side effects if the yet unproven hypothesis of the side effects being energy related.

SELECTIVE LASER TRABECULOPLASTY AND TARGETING

The typical SLT procedure uses a manually aligned gonioscopic contact lens to deliver ~100 nonoverlapping laser pulses from a Q-switched frequency-doubled Nd:YAG laser to the entire 360 degrees of the TM. Commonly, the energy setting is determined using the method described by Latina et al[16] in 1998: starting at 0.8 mJ and titrating to the lowest energy where champagne-like cavitation bubbles are produced and then reducing the energy by 0.1 mJ. The scientific basis of this titration and its usefulness has not been proven.[17] Such titration may happen multiple times during a procedure. Therefore, the ability to eliminate this titration protocol would allow for an easier and more standardized SLT procedure. The basis for the 0.1 mJ steps is not readily known.

Adjusting the energy level for each and every spot is impractical, particularly since laser shots are expended to determine the final titration level, that is, some shots will be at a higher or lower energy, while the operator is undertaking the titration. This is particularly the case among patients with uneven pigmentation at the TM. Some clinicians have suggested that bubbles are not ideal on every shot, but every 2 or 3.[18,19] In addition, in common practice precise targeting of the TM does not always occur, which results in a change to the energy that actually reaches the TM and could result in energy impacting other tissues.

Additional variability in energy introduction to the target tissue is introduced by the gonioscope, which must be manually positioned on the ocular surface. The difficulty of manually aligning the gonioscope can be demonstrated by a study that reported training on a simulator. For the untrained cohort, ~50% of the spots were not placed correctly versus about 8% for those receiving the training.[20] Thus, it is likely that "precise energy" reaching the TM does not always occur in practice due to targeting errors, which are commonly observed clinically. To date, there has been no proven relationship between SLT effectiveness and the laser pulse energy[12] or a relationship between cavitation bubbles and tissue changes.[17,21] Therefore, attempts to precisely adjust the laser energy may not have a clinically significant benefit.[12]

Tissue Alterations Resulting From Selective Laser Trabeculoplasty

Several studies have examined SLT-induced TM structural changes. These studies have been prompted by the fact that using the much higher energy argon laser trabeculoplasty results in collagen and tissue contraction.[22]

In vivo histologic SLT studies in human eyes are rare, as such studies typically require scheduled enucleation. In one such study involving 3 human eyes, SLT was performed using a gonioscope and a 0.7 mJ laser energy setting. Histology of the enucleated eyes 1–5 days after the SLT procedure showed cellular changes throughout the entire thickness of the TM but not extending into the scleral stroma. The cellular lining of the Schlemm canal wall was disturbed, cell nuclei were condensed and elongated, and intracellular pigment granules were found in the TM. There was a minor disruption to the trabecular beams visible on electron microscopy.[23] Similar results were found in a more recent study of one enucleated eye using 1 mJ pulses of both 1 ns or 3 ns duration in different hemispheres, with similar results for both pulse durations.[24] Both in vivo studies showed minor collagen fiber changes occurring in 0.7 mJ or 1.0 mJ.

Other studies have been performed ex vivo with the TM removed from the eye. Unlike the typical clinical situation in which the laser is delivered through a gonioscope in contact with the cornea and striking the TM at a very oblique angle with a concomitant increase in the spot size (Fig. 1), in these ex vivo studies, the laser was delivered perpendicular to the surface (90 degrees incident angle) of the excised sample. The actual spot delivered to the TM tissue was, therefore, a true 400 μm circle as opposed to the lengthening that occurs in SLT delivery at a high angle of incidence due to the angle of the gonioscope-delivered beam. Thus, the energy density, or fluence (energy per spot area), in the ex vivo cases was substantially higher than seen in in vivo cases. In Appendix 2 (Supplemental Digital Content 1, http://links.lww.com/IJG/A844), we estimate that the fluence on the TM in the ex vivo studies with the laser at normal incidence is about 6× higher than delivered in SLT with a gonioscope due to spot size elongation (3× reduction) and transmission losses (2× reduction) through the cornea and anterior chamber. Thus the total energy delivered to the TM in ex vivo experiments to the samples is estimated to be 3× higher than in SLT due to transmission losses (2× reduction) and the spot being larger than the TM (1.5× reduction). In the reported results of the ex vivo cases, the laser effects observed may have resulted in significantly overestimated histologic effects of the laser as compared with the fluences actually delivered to the TM at the SLT device energy settings used.

In vitro cellular studies using cultured bovine TM cells, with a laser at normal incidence resulting in 400 μm on the tissue, have been performed.[26,27] In these studies pigmented cells were prepared by infusing melanin granules into nonpigmented cells. Interestingly, the laser intensity required to show a visible change in the cells occurred at levels 3 to 4 times lower than the authors expected,[27] corresponding to an SLT energy device setting of 0.2 mJ using the mentioned conversion ratios. This comparison supports the concept of the effectiveness of SLT using low energies that have been observed in SLT studies, assuming a correspondence between in vitro and in vivo cellular studies.[12]

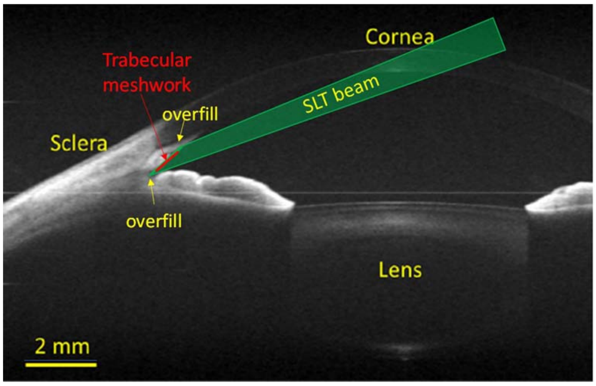

FIGURE 1. OCT[25] image of anterior chamber superimposed with SLT beam to scale. The convergence angle of the SLT beam is shown as a typical 3-degree full angle. The 400 μm spot diameter is effectively elongated at the TM by the high angle of incidence. The energy loss from the "overfilled" spot by irradiation of tissue beyond the TM is indicated graphically. OCT indicates optical coherence tomography; SLT, selective laser trabeculoplasty; TM, trabecular meshwork.

In another study, cell death occurred at very low fluence (incident energy/laser spot area) levels of 0.018 J/cm^2 in highly melanin-infused cells.[26] This value is equivalent to an output laser energy value of 0.07 mJ from an SLT laser. If cell death in the TM is required for IOP reduction in SLT, then this estimated equivalent energy of 0.07 mJ may be around the threshold energy[12] for IOP reduction. Such a value is below the available ranges of standard SLT device energy settings summarized in Table 1 and would be lower than all energy values reported in a recent SLT survey.[12]

In a study using ex vivo human cadaver excised TM segments, exposure with 1 mJ from an SLT laser at normal incidence (6 mJ SLT procedure equivalent ex device) showed no evidence of coagulative damage or disruption to the TM. The only ultrastructural evidence of the laser effect was the cracking of intracytoplasmic pigment granules and the disruption of trabecular endothelial cells.[28] In another study, structural changes were seen only at 2.0 mJ or 12.0 mJ SLT equivalent energy using scanning electron microscopy. The structural damage observed was not related to the appearance of champagne bubbles.[21] At the lowest energy, 0.4 mJ (2.4 mJ SLT procedure equivalent due to spot elongation and transmission loss), transmission electron microscopy showed only disrupted TM cells with cracked and extracellular pigment granules.[21] Furthermore, these studies showed no TM structural collagen fiber damage occurs below 3.0 mJ SLT procedure equivalent ex device, which is the highest energy output of SLT devices listed in Table 1.

In summary, the SLT energy delivered to the TM seems to cause mainly cellular changes. Changes to the TM structure have been observed as minimal in 2 in vivo studies using 0.7 mJ and 1.0 mJ, and in ex vivo studies changes occurred at SLT laser energies far exceeding the maximal settings of a commercial device. This discrepancy in energy required for altering the collagen structure may be due to a healing response to damaged tissue not visible on electron microscopy, thus explaining the in vivo changes on lower energy. A possible energy for SLT effectiveness may be 0.07 mJ, as implied by the ex vivo cell culture experiments described previously. Thus, lower SLT energy may mitigate tissue changes seen at higher energies, yet these lower energies may be well above the threshold energy level required for its clinical effectiveness in IOP reduction.[11]

Variation in Selective Laser Trabeculoplasty Laser Parameters: Do We Need Precise Titration?

In this section, we survey the characteristics of approved available SLT lasers and discuss the inherent energy and energy density variations inherent in this type of laser. The variability between systems and the intrinsic variability of laser outputs within a particular system together with the known effectiveness of SLT systems in general suggests that a significant range of laser parameters are likely to result in effective IOP reduction. The effectiveness of SLT procedures despite these variations suggests that precise energy titration may not be required.

A partial list of commercial nanosecond SLT devices is presented in Table 1. The laser pulse duration varies between 1 ns and 4 ns. Laser intensity is inversely proportional to the pulse duration, so a 1 ns laser would have four times higher intensity than a 4 ns laser for a given device energy setting (more completely, intensity is energy per area per pulse duration). The existence of a 4X range in pulse duration suggests that precise pulse duration is not important. As a possible example of the relative independence of SLT efficacy on precise pulse duration, one study comparing SLT of a 1 ns laser to a 3 ns laser arrived at the same laser pulse energy for each duration using the champagne bubble titration technique, with similar IOP reduction.[24] The important parameter may be energy density, or fluence, for pulses between 1 ns and 3 ns, which would be consistent with a thermal effect, even though the intensity is different by a factor of 3 in this study or a factor of 4 when considering the lasers in Table 1.

TABLE 1. A Partial List of Commercial SLT Laser Devices (400 μm Spot Size)

Manufacturer	Model	Pulse duration (ns)	Beam profile	Energy range (mJ)
Ellex	Tango	3	Super-Gaussian	0.3–2.6
Lumenis	SELECTA Duet / Trio	3	Super-Gaussian	0.3–2.0
Lightmed	LIGHTLas SLT Duex	3	Diffraction-limited	0.2–2.6
Nidek	YC-200 S plus	3	Not found	0.3–3.0
Optotek	OptoSLT nano	1	Not found	0.2–2.0
Optotek	OptoYAG&SLT M	4	Not found	0.2–2.6
Quantel	Optimis Fusion	4	Homogeneous spot	0.3–2.0
Quantel	SoLuTis	4	Top hat	0.2–2.0
ARC	CITO 532	3	Homogeneous spot	0.2–2.0

SLT indicates selective laser trabeculoplasty.

The common, commercially available SLT laser systems are listed in Table 1, with the main parameters of the pulse duration, available output pulse energy, and beam profile (ie, a descriptor for the spot shape seen in a cross-section of the laser beam at the beam focus). The Table 1 beam profiles vary from a Gaussian shape resembling a bell curve (inferred from the manufacturer's specification of a diffraction-limited spot) to a homogenous spot (not well-defined but presumed to have some transverse intensity profile that is uniform). Figure 2 provides an example of 2 types of beam intensity profiles.

All lasers in Table 1 also specify a 400 μm spot at the target, although the measurement criteria of the actual spot size measurement, for which the device is calibrated in air, is not typically revealed by manufacturers. The actual spot size, therefore, probably varies between SLT units as the following examples suggest for which user manuals were found. In one system, the beam size was defined to be the diameter enclosing 84% of the laser energy, and in another system, the spot size is the size of the mark made by the beam on laser burn paper. The relationship between these measurements is not clear, especially since the beam does not have well-defined edges. In addition, when the laser is delivered to the TM, the oblique angle of incidence certainly changes the effective spot size. Even when different SLT lasers have the same energy setting, the energy density on the TM will depend on the effective spot size on the TM tissue and the beam profile (the distribution of energy within the spot). As an example, a Gaussian beam has a high central peak, whereas the super-Gaussian beam is flatter and more uniform over the entire spot. Two lasers with the same pulse energy can, therefore, deliver significantly different energy densities within the laser spot. An ideal Gaussian beam will have a peak energy density twice as high as an ideal top hat beam (cylinder) with the same energy and spot size.[29] Also, note that the so-called super-Gaussian beam has deep ripples in the beam that cause local intensity variations or "hot spots" as seen in Figure 2. Clearly, the TM on which the laser beam impinges impacted is not uniformly irradiated. Such hot spots produce locally high beam intensities and may be the locations where bubbles may actually form, bringing into question what titrating to a laser hot spot accomplishes since the intensity clearly varies significantly across the irradiated section of TM.

Within a specific laser, there are inherent beam parameter fluctuations in beam profile and energy, in consecutive applications, even when the laser settings are not changed. For example, Figure 3 shows the beam profiles (an intensity plot) of several consecutive laser shots at the same energy setting measured from a commercial SLT laser. Each laser pulse has a unique beam profile and each laser shot has different intensity peaks and valleys, and hence, different hot spots. The intensity and energy density within the laser spot are not uniform but change from shot to shot. Not only does the beam profile of a specific laser change but the actual energy within the laser pulse fluctuates from one shot to the next. The international standard for lasers[30] permits energy fluctuations of ± 20% and up to +50% for "excessive laser output limit" from the set value meaning that a typical SLT 1.0 mJ pulse could lie between 0.8 mJ and 1.5 mJ energy settings on the same device and between different devices, making any 0.1 mJ titration adjustment procedure not reliably repeatable.

Clearly, there is a wide variation of laser parameters in commercially available SLT lasers, and each specific laser will show variability in the energy, spatial profile, and fluence of the target tissue. Beyond variability, other laser trabeculoplasty procedures (Appendix 1, Supplemental Digital Content 1, http://links.lww.com/IJG/A844) have a variety of laser parameters, but all result in a reduction of IOP. Despite this variability, SLT is generally safe and effective.

Furthermore, spatial variations within the laser spot and the optically nonhomogenous TM tissue produce local hot spots. It is reasonable to hypothesize that such hot spots are the locations where bubble formation occurs, and that bubble formation may be related to localized peak intensities in the spot rather than the overall pulse energy delivered. This possibility suggests that the actual mechanisms giving rise to bubble formation during the bubble titration method are not well understood and may not be indicative of procedure success or efficacy.

DISCUSSION

The mechanism of action of SLT was initially thought to be selective light absorption in melanin granules. This was perhaps reinforced by the observation that melanin granules can be easily seen in histology. However, no

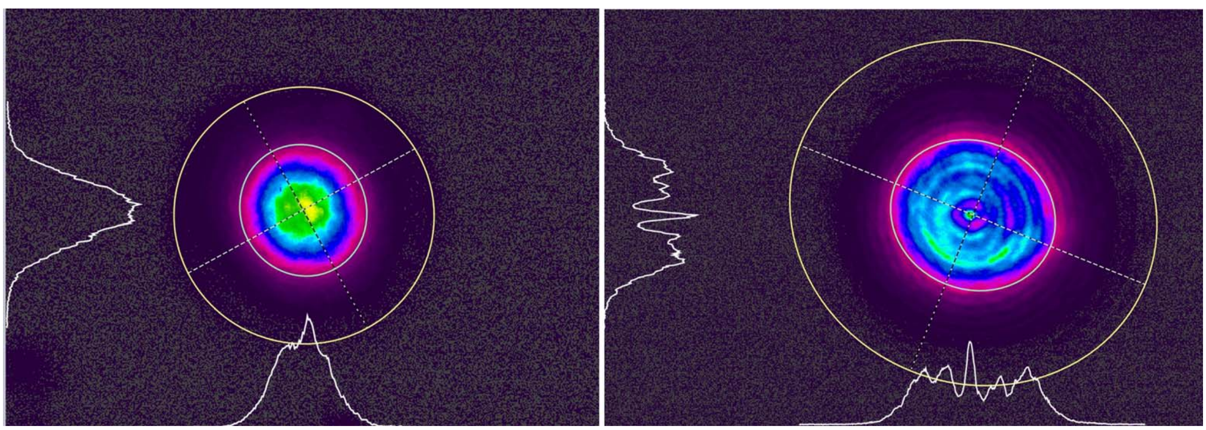

FIGURE 2. False color Intensity maps and intensity plots of beam profiles measured along orthogonal planes (dotted lines) of SLT spots imaged at the visible aiming beam focus locations. Colors denote intensity. Beam lineouts along the axis of the spot are shown on the left and bottom of each plot. The Gaussian beam profile of a laboratory laser (left) and the so-called "super-Gaussian" beam profile of a commercial SLT laser measured in the target plane (right). SLT indicates selective laser trabeculoplasty.

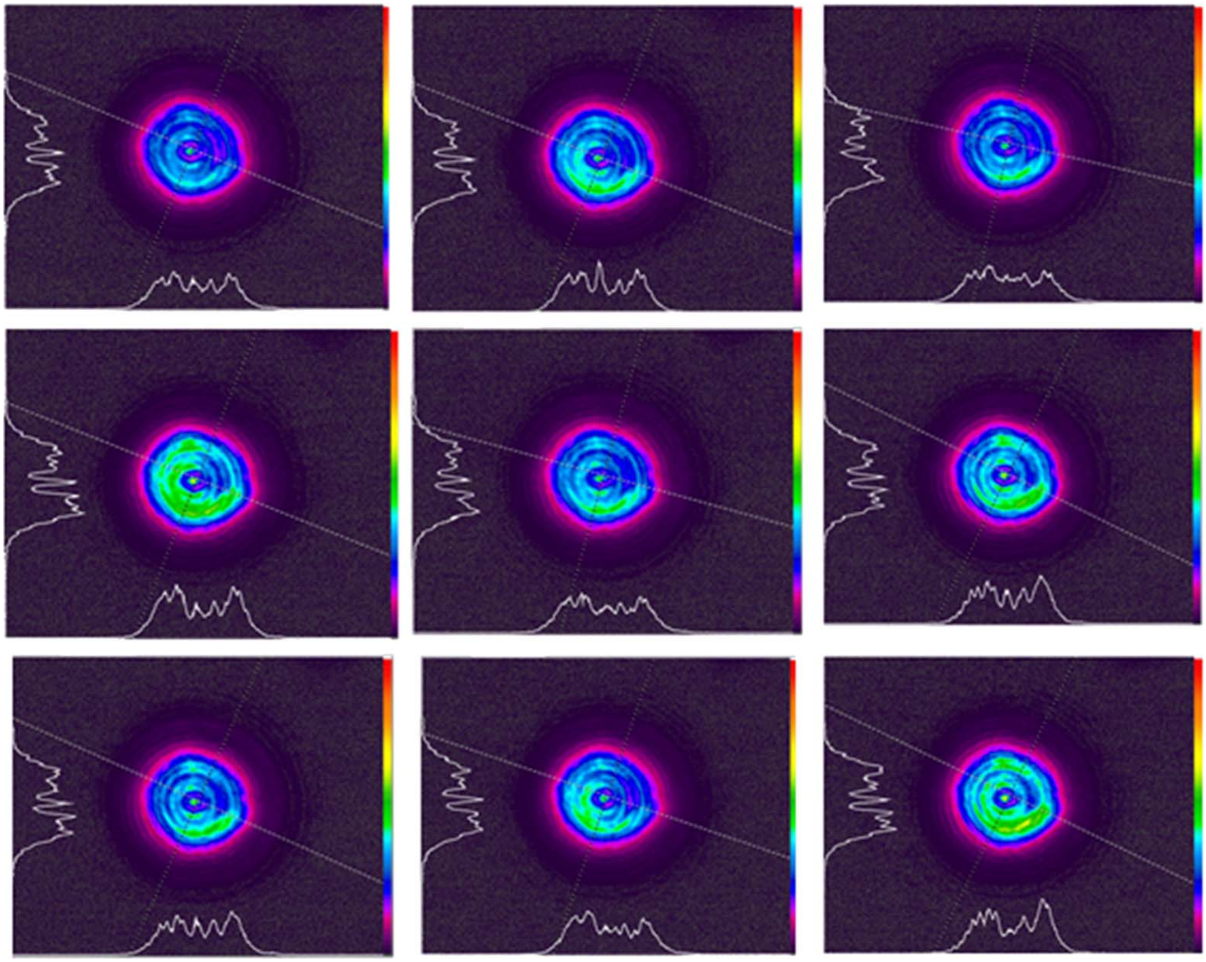

FIGURE 3. Beam profiles for different laser shots emitted by the same laser operating with the same nominal settings.

correlation between TM pigmentation and IOP reduction has been demonstrated.[12] Furthermore, prospective randomized controlled trials have not been associated with any serious adverse events, and the concern is that post-SLT pressure spikes in heavily pigmented TMs might result in severe long-term side effects. This has only been reported in 9 cases out of millions of treated patients. In addition, it is not clear that the long-term effects seen in this study were due solely to the SLT treatment.[31] The authors note that it is widely accepted that such cases do occur and are believed to be commonly seen clinically regardless of the SLT treatment.

Consistent laser energy delivery to the TM does not always occur in practice due to the pulses used to perform the titration (under or over energy), the position of the lens, and the ability of the operator to align the beam precisely to the TM. SLT seems to cause mainly cellular changes resulting in IOP reduction. In vitro studies have shown that 2.0 mJ can result in a structural TM change,[21] but in the clinical situation, this correlates to energies much beyond the 3.0 mJ limit on clinical SLT devices. In vivo studies have shown changes to the trabecular beams at energies of 0.7 and 1.0 mJ which may in part be due to a healing response.[23,24] Thus using lower energy may mitigate irreversible tissue damage and acute side effects. The success of IOP lowering on repeat SLT treatments would seem to indicate the inherent safety of this procedure.[7,8,13,32–42]

The IOP reduction is likely to be determined by the fluence associated with nanosecond SLT pulses. However, the fluence for different commercially available SLT lasers can vary by a factor of 2 or more. Even for a given energy setting on the laser device, fluctuations in the laser output do occur. Energy density fluctuations within the laser spot will be much larger than energy variations as the spot shape may change between each laser shot. Adjusting the SLT energy in increments of 0.1 mJ with or without the appearance of champagne bubbles seems to have limited practical meaning given the fluctuations in laser energy, beam profile, and fluence. In addition, there is no known correlation between the appearance of bubbles and TM structural changes.[21] Furthermore, the hypothesis that bubbles are produced at local hot spots within the laser spot and that changes from shot to shot may explain why bubble titration and procedure efficacy may not be correlated.

SLT seems to be an inherently robust treatment despite the variations of energy reaching the TM due to operator delivery, intrinsic laser fluctuations, and the variation in laser parameters between SLT commercial devices. An insensitivity to energy changes within a relatively broad range would appear to indicate that SLT is a threshold process. In such a process, for pulse energies exceeding a critical value (perhaps as low as 0.07 mJ as discussed, or 0.3 mJ as reported for successful IOP reduction[15]) then a treatment effect—manifested as IOP reduction—will occur.

CONCLUSIONS

The IOP lowering effects of SLT treatments seem to be insensitive to the overall intensity in an SLT laser spot (as evidenced by the results of clinical trials[12]), insensitive to the variations between commercially available (nanosecond) SLT laser beam properties, and insensitive to variations caused by beam delivery and inherent fluctuations in the laser. In addition, champagne bubble formation has not been shown to be related to IOP-lowering results.[21]

Whereas, no direct relationship between laser energy and IOP reduction or energy and side effects has yet been reported. We propose that the effect of SLT energy on IOP is a threshold phenomenon in which a single low-energy dose may suffice to achieve an adequate effect on IOP. Disregarding the champagne bubble dosimetry and using a single, low-energy beam may simplify and shorten the procedure considerably. It is not certain that the precise SLT dose-response relationship could be tested by a suitably powered, prospective randomized controlled clinical trial is possible, given the inherent variations in energy delivered to the TM in the SLT procedure.

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