Laser Trabeculoplasty

Is there still a place for the argon laser in glaucoma therapy?

By Hylton R. Mayer, MD

This article reviews the historical role of argon laser trabeculoplasty (ALT) as well as its current indications and usage in the management of patients with glaucoma.

Laser trabeculoplasty (LTP) has been a therapeutic option for the management of glaucoma for approximately 30 years, with its popularity rising during the past 10 years (Figure 1). LTP is attractive as a therapeutic option, because it can complement or supplant topical medical therapy. One laser treatment session can reduce the IOP for years, thus eliminating the side effects or poor compliance associated with medication. Additionally, LTP is typically a well-tolerated and generally low-risk procedure, especially compared with incisional glaucoma surgery.

ALT is the prototypical procedure against which other LTP modalities are measured. Compared with other medical, laser, and incisional surgical options, ALT possesses numerous advantages but also shortcomings. By and large, the various alternative LTP modalities available today were developed to address those limitations and/or disadvantages.

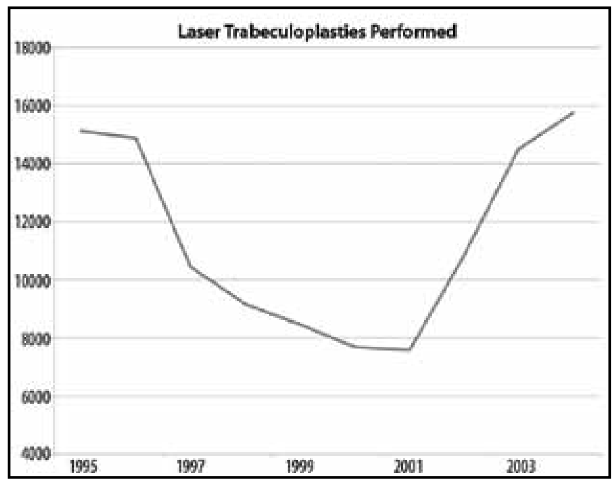

Figure 1. The number of laser trabeculoplasties performed from 1994 to 2004. Adapted from Ramulu PY, Corcoran KJ, Corcoran SL, Robin AL. Utilization of various glaucoma surgeries and procedures in Medicare beneficiaries from 1995 to 2004. *Ophthalmology*. 2007;114(12):2265-2270.

ARGON LASER TRABECULOPLASTY

Wise and Witter are typically credited with demonstrating the first effective method for LTP in 1979.[1] The original, and classically utilized, energy source for modern LTP was the continuous-wave argon laser, operated in the blue-green wavelength spectrum (454-529 nm). Although numerous early case series supported the tolerability and efficacy of ALT, in 1990, the Glaucoma Laser Trial (GLT), a study sponsored by the National Eye Institute, demonstrated that the laser procedure was at least as efficacious as topical medical therapy.[2]

Numerous studies have aimed to identify the pathophysiologic changes that ALT induces. The exact mechanism by which the procedure works remains unknown, but it is commonly believed that the laser energy applied to the trabecular meshwork initiates structural and/or physiologic changes that promote aqueous outflow.[3] Microscopic and immunohistochemical analysis of the trabecular meshwork after ALT have identified local photocoagulation of directly treated trabecular tissue, while trabecular cells adjacent to treated areas have demonstrated increased phagocytic activity (Figure 2). Additionally, studies have recognized changes in the extracellular matrix after ALT related to an induction of matrix metalloproteinases.

INDICATIONS AND CONTRAINDICATIONS

ALT is appropriate for the treatment of primary open-angle glaucoma (OAG) and certain secondary forms of OAG. The procedure is particularly effective for pigmentary and pseudoexfoliation glaucomas.[4,5] Although ALT has classically been used after the failure of topical IOP-lowering medications (whether due to ineffectiveness, "A significant strength of ALT is the extent and longevity of published data regarding the procedure."

patients' intolerance, or their inadequate compliance with the prescribed medical regimen), numerous studies have identified the procedure as a safe and efficacious primary or early therapy.[6] For example, patients in the GLT were randomized to receive medical therapy or primary laser therapy. Researchers found that patients who received ALT had lower pressures, less visual field loss, and less optic disc damage than those who were started on medication.[2]

ALT is relatively contraindicated in uveitic OAG, because the laser energy can induce or exacerbate ocular inflammation. Contraindications for ALT include scenarios where anterior chamber angle structures cannot be visualized or identified or eyes with little or no trabecular meshwork pigmentation. ALT generally is not effective in patients with traumatic glaucoma, juvenile OAG, or glaucoma due to elevated episcleral venous pressure. Several studies have shown the procedure to have a limited effect in patients who have undergone previous ALT.[7] It should be used with substantial caution in patients who have very high initial IOPs, due to the risk for IOP spikes after laser treatment. ALT also should not be used for patients with target IOPs that are under episcleral venous pressure.

TREATMENT PROTOCOL

Typical periprocedural care involves IOP-lowering drops such as apraclonidine 1% or brimonidine 0.2%, instilled 30 to 60 minutes preoperatively, to reduce postprocedural IOP spikes. Pilocarpine 4% may improve the surgeon's access to angle structures as well as mitigate postoperative elevations in IOP. A typical ALT treatment protocol would involve 100 spots delivered over 360° of the anterior trabecular meshwork. Dividing the total treatment over multiple sessions, separated by days or weeks (eg, two 180° applications performed 2 weeks apart) may reduce postoperative spikes in IOP.

Typical postoperative care usually involves checking the IOP about an hour after the procedure. It may be necessary to check the IOP 1 day postoperatively in patients with significant IOP elevation or those with advanced glaucomatous damage who are at increased risk of damage from IOP spikes. Surgeons commonly prescribe a topical steroid such as prednisolone acetate 1% to control postoperative inflammation and have patients continue their use of IOP-lowering medications. The final IOP-lowering effect after ALT is expected about 1 month postoperatively.

(Courtesy of Steven D. Vold, MD.)

Figure 2. Blanching of the trabecular meshwork after ALT.

PUBLISHED FINDINGS

A significant strength of ALT is the extent and longevity of published data regarding the procedure (a PubMed search for *argon laser trabeculoplasty* results in more than 400 articles). Published studies related to ALT include OAG, normal-tension glaucoma, and secondary OAG (pigmentary, pseudoexfoliation, and steroid-responsive glaucomas, to name a few). They cover immediate pressure response, variations in laser-application technique, repeat treatment, diurnal curve, ALT's role as initial therapy for glaucoma, and its comparison to selective laser trabeculoplasty (SLT). Research has also dealt with the effect of the number of laser burns, postural behavior, the perioperative use of a corticosteroid or a nonsteroidal anti-inflammatory drug, various IOP-lowering medications, and ALT's performance by residents. In addition, investigators have assessed the procedure's effect on endothelial cells, visual field progression, various ethnic groups, and the rates and success of trabeculectomy. The research has included numerous 1-, 3-, 5-, and 10-year studies; histologic and pathophysiologic studies; and multicenter studies sponsored by the National Eye Institute, including the GLT, Advanced Glaucoma Intervention Study (AGIS),[8] Early Manifest Glaucoma Trial (EMGT),[9] and Collaborative Initial Glaucoma Treatment Study (CIGTS).[10]

Besides the volume of literature related to its use, ALT has several other advantages compared with the current generation of trabeculoplasty lasers. For one, argon lasers can be used for a variety of ophthalmic applications, including retinal photocoagulation, iridoplasty, and suture lysis. Moreover, their multifunctionality and generally wide availability make them cost-effective.

LIMITATIONS AND DISADVANTAGES

General concerns with ALT include its potential to cause inflammation, the possibility for peripheral anterior synechiae to develop (particularly if laser energy is applied to posterior angle structures), and the relatively high risk for temporary or sustained IOP spikes. In the GLT, 30% of patients experienced an increase in IOP of 5 mm Hg, and 12% had a rise greater than 10 mm Hg (vs about 24% and 6% with increases of 5 and 10 mm Hg or more, respectively, after SLT).[2,11] A major concern with ALT is that classic laser setting parameters result in photocoagulation of viable trabecular meshwork tissue.[12] The destruction of portions of trabecular meshwork tissue may contribute to the higher rates of IOP spikes after ALT as well as the procedure's lack of repeatability.

SUMMARY

A recently published review by the American Academy of Ophthalmology affirmed that LTP successfully lowers IOP.[13] The report noted that, although the most substantial evidence supports ALT's efficacy, a growing body of literature supports SLT's effectiveness and repeatability. Currently, however, there is inadequate published literature to identify a single superior modality of LTP. Although the popularity of numerous options for LTP is increasing, ALT has a proven track record of safety and performance, and it remains an excellent treatment option for many glaucoma patients.

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Ten years of experience have revealed much about selective laser treatment.

By Brian A. Francis, MD, MS

Surgeons now have 10 years' experience with selective laser trabeculoplasty (SLT) to lower the IOP in patients with open-angle glaucoma. Several points have emerged during the past decade that were not evident when the procedure was introduced. They are SLT's mechanism of action, its utility as initial and replacement therapy, and the repeatability of treatment.

MECHANISM OF ACTION

Laser trabeculoplasty is one of the few glaucoma treatments that address the key problem in open-angle glaucoma: decreased trabecular outflow facility. There are several theories on how the procedure exerts this effect, but general consensus holds that it is a biological response. Studies of SLT by Alvarado using flow experiments and endothelial cells cultured from the trabecular meshwork (TM) and Schlemm canal have examined this issue. Laser trabeculoplasty initiates a signaling cascade between the cells in the TM and those in Schlemm canal. Monocytes are recruited, become macrophages, and may be a mechanism for clearing obstructive particulate matter from the system. In addition, the signaling system involves key factors such as cytokines released by endothelial cells in the TM. These cytokines move with the aqueous and then bind to the outflow barrier, which is formed by the endothelial cells in Schlemm canal. Laser trabeculoplasty's effect on cellular junctions and possibly cytoskeletal changes increase the outflow facility. Interestingly, these studies also postulate that SLT's cellular effect is the same as that of prostaglandin analogues.[1-4]

INITIAL THERAPY

SLT is the first laser trabeculoplasty procedure to gain widespread use as initial treatment for glaucoma. The reason likely relates to the minimal tissue damage it causes to the angle due to its very short duration relative to the thermal relaxation time of the TM. Several clinical trials have shown SLT to reduce the IOP by approximately 30%.[5-9] This decrease is equal to that expected from therapy with prostaglandin analogues, which are currently the most potent class of topical glaucoma medication. Randomized trials have demonstrated equivalent IOP lowering with SLT and prostaglandin analogues when they are used as primary therapy.[5,7] Moreover, both SLT and latanoprost significantly reduce fluctuations in IOP.[10] Clinicians generally agree that, as with medication, SLT is most efficacious when used primarily and that its effect diminishes when greater numbers of medication are used concurrently.

REPLACEMENT THERAPY

A majority of glaucoma patients' IOPs are controlled with medication. Only a minority has uncontrolled disease or is naïve to treatment. Several studies have assessed SLT as a replacement for medical therapy in this medically controlled group. In a prospective trial, SLT allowed a reduction of topical glaucoma medication while maintaining the target IOP.[11] This finding may be especially important for patients who are using multiple topical drops, have problems adhering to prescribed medical therapy, cannot afford medication, or have intolerable side effects from medical therapy.

REPEATABILITY

In SLT, selectivity depends on the brief application of laser energy and the targeting of only pigmented cells within the TM. These characteristics led to the hypothesis that the procedure could be performed after previous argon laser trabeculoplasty (ALT) or repeated after prior SLT. In contrast, retreatment with ALT is contraindicated, because its coagulative effect causes scarring of the TM. If the procedure were to be repeated over the same area, scarring would eventually decrease outflow facility.

In the initial clinical trial of SLT, Latina and colleagues found that the procedure successfully lowered IOP even in eyes that had previously undergone ALT but had subsequently stopped responding to that treatment.[12] True repeatability, however, requires that SLT be performed once over 360º of the TM and effectively lower the IOP. This response would then wear off over time, and the procedure would be repeated over 360º to achieve a similar IOP-lowering response. A study by Hong et al showed that the decrease in IOP was similar after the first and second treatments when SLT was performed in this manner.[13] A larger study presented as an abstract also showed a similar reduction in IOP with the first and second performances of SLT, although there was a lower baseline measurement in the second group. A subanalysis of equal baselines, however, showed an equal reduction in IOP between the two groups.[14]

> "Surgeons' experience with SLT during the past decade has proven its effectiveness as primary therapy."

CONCLUSION

Basic scientific studies have explored SLT's mechanism of action and shown the complex signaling pathway between cells in the TM and Schlemm canal that increases outflow facility. This biological response is likely similar for other laser trabeculoplasty procedures. It may also be a method by which some glaucoma medications and perhaps phacoemulsification cataract surgery lower IOP. Surgeons' experience with SLT during the past decade has proven its effectiveness as primary therapy, as replacement therapy to reduce patients' dependence on glaucoma medication, and as adjunctive treatment for medically uncontrolled glaucoma. It appears that SLT can be repeated at least once and perhaps several times with equal efficacy.

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Treatment with a diode laser appears to lower IOP while minimizing complications.

By Jeffrey A. Kammer, MD

Laser trabeculoplasty was first noted to reduce IOP in the early 1970s,[1,2] but it was Wise and Witter's landmark study in 1979 that popularized argon laser trabeculoplasty (ALT) as an effective treatment for multiple forms of open-angle glaucoma.[3] Since then, several studies have corroborated the efficacy of laser trabeculoplasty, including three landmark trials sponsored by the National Eye Institute: the Advanced Glaucoma Intervention Study (AGIS), Early Manifest Glaucoma Trial (EMGT), and Glaucoma Laser Trial (GLT).

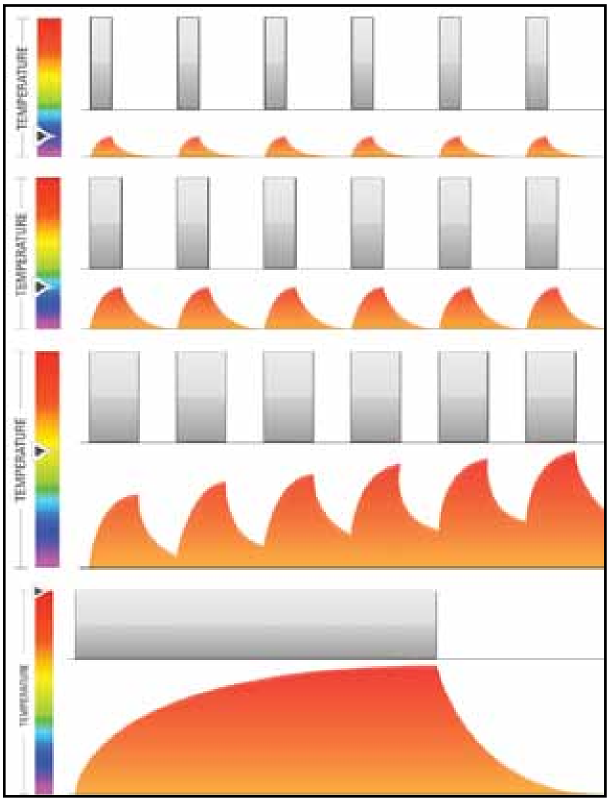
Despite strong evidence to support the use of ALT early in the disease process,[4] the procedure has largely been reserved for refractory cases of glaucoma due to ALT's undesirable side effects and collateral damage from trabecular disruption induced by the argon laser (ie, postoperative inflammation, elevated IOP, formation of peripheral anterior synechiae, and scarring of the trabecular meshwork [TM]).

In an effort to harness ALT's ability to reduce IOP but minimize its associated complications, Mark Latina, MD, developed selective laser trabeculoplasty (SLT). In this procedure, a frequency-doubled, short-pulsed (Q-switched) Nd:YAG laser selectively affects melanotic elements within the TM according to the principles of photothermolysis.[5] SLT exerts an excellent hypotensive effect while maintaining trabecular integrity. Unfortunately, the procedure still produces an anterior chamber reaction and an occasional post-treatment rise in IOP. Research into other options for laser trabeculoplasty has therefore continued, and one alternative uses a diode laser.

THE EVOLUTION OF DIODE LASER TRABECULOPLASTY

In the early 1990s, researchers demonstrated that diode laser trabeculoplasty (DLT) could effectively lower IOP.[6] Moreover, a 5-year, randomized, prospective trial comparing ALT and DLT found no statistically significant differences in IOP lowering between the two groups at any time interval. Although both procedures were effective and well tolerated, they caused a few cases of peripheral anterior synechiae.[7]

Efforts to reduce destruction resulted in the use of subthreshold micropulse diode laser energy, with work pioneered by retinologists[8,9] and later adapted by glaucomatologists. Micropulse diode laser trabeculoplasty (MDLT) is a large-spot, low-irradiance treatment. An 810-nm diode laser emits a series of short, repetitive, near-infrared pulses. The brief duration of pulses confines the thermal effect to the absorbing melanosomes, with minimal diffusion of heat to the adjacent tissues. The cooling period is proportionately longer than the pulse time, thus allowing the thermal relaxation of tissue with equilibration toward baseline temperature. Each micropulse elevates the temperature of the cell enough to denature proteins but not so high as to cause coagulation necrosis.[10]



(Courtesy of Iridex Corporation.)

Figure. In conventional, continuous-wave photocoagulation, a rapid rise in the temperature of the targeted tissue creates blanching and a high thermal spread. MicroPulse technology (Iridex Corporation) finely controls thermal elevation by "chopping" a continuous-wave laser beam into a train of short, repetitive pulses that allows tissue to cool between pulses and reduces thermal buildup.

TECHNIQUE

The diode laser (IQ 810; Iridex Corporation) is compact, portable, and solid state with a slit-lamp adapter for use in trabeculoplasty. There is no consensus on treatment parameters, but the most common settings for MDLT are a 300-µm spot diameter, 2,000-mW power, a 200-millisecond exposure time, and a 15% duty cycle. With these settings, a train of 100 micropulses is delivered to the eye with 300 microseconds of "on" time, each separated by 1,700 microseconds of "off" time (Figure). Although most protocols recommend performing 60 to 65 applications over 180º, a few surgeons prefer to deliver 120 to 130 spots over 360º. The laser's longer extinction length compared with SLT enables deeper penetration into the TM, thus facilitating the laser's interaction with tissue down to the cribriform layer.[11]

MECHANISM OF ACTION

The laser energy delivered to the TM by MDLT does not produce a visible clinical change such as the blanching of tissue or the formation of bubbles. The effect of treatment was demonstrated by a histopathologic evaluation of autopsic eyes that had recently undergone ALT, SLT, and MDLT. In this study, craters had formed in the ALT eyes, whereas the SLT and MDLT eyes had entirely intact TMs, save for mild flattening of the trabecular beams in the MDLT eyes.[12]

As with other forms of laser trabeculoplasty, the exact mechanism by which MDLT lowers the IOP is incompletely understood. The most likely theory is that sublethal photothermal stimulation elicits a therapeutic stress response from the TM cells—the release of a host of cytokines (including interleukin-1β, tumor necrosis factor-α, and heat shock protein 27) and matrix metalloproteinases—which increases outflow facility.[13-15]

EFFICACY

In 1990, McHugh et al first established DLT as an effective tool with which to lower IOP in patients with primary open-angle glaucoma or ocular hypertension. This prospective pilot study reported a 33% reduction in IOP at 6 months.[16] Although the results are compelling, the study's small sample size, short follow-up, and noncomparative nature must be taken into consideration. The results of a randomized, prospective clinical trial comparing DLT and ALT also documented a 33% IOP reduction for DLT at the 5-year point. Furthermore, this study confirmed that DLT is just as effective at lowering IOP as ALT over a 5-year period.[17]

Ingvoldstad et al first demonstrated the IOP-lowering efficacy of MDLT in a prospective, randomized trial that compared the procedure's effect on pressure with that of ALT. The investigators documented an 18.3% and 18.9% drop in IOP after MDLT and ALT, respectively, at the 3-month postoperative visit.[18]

Detry-Morel et al published the first article detailing the short-term comparative efficacy and safety of MDLT and ALT. In their prospective, randomized study, the mean reduction in IOP (2.5 mm Hg in MDLT patients vs 4.9 mm Hg in ALT patients) and percentage of IOP reduction (12.2% for MDLT patients vs 21.8% for ALT patients) were significantly more robust in the ALT group 3 months after treatment. That said, the number of medications required at the final visit was significantly lower in the MDLT cohort. Anterior chamber inflammation was minimal in both groups, with no significant difference.[19]

Fea et al published a prospective noncomparative interventional case series of 32 consecutive eyes of 20 patients with open-angle glaucoma who underwent MDLT. The purpose of the study was to evaluate the procedure's pressure-lowering efficacy over a follow-up period of 12 months. In the eyes that responded to treatment, IOP decreased 5.5 mm Hg on average, which represented a 21.3% reduction compared with baseline There was no significant increase in mean flare values based on readings by the Laser Flare Meter (Kowa Company, Ltd.), and only one eye experienced a significant postoperative elevation of IOP. MDLT was well tolerated by the patients.[20]

Among the few published studies on MDLT, the article by Rantala and Valimaki is the only one to question the procedure's efficacy. In their study, 2.5% of the treated patients experienced a decrease in IOP of 20% or more, and 7.5% achieved a drop in IOP of at least 3 mm Hg. On a positive note, there were no complications, and anterior chamber inflammation was negligible.[21]

CONCLUSION

At this time, the preponderance of data suggests that MDLT is an effective means of lowering IOP. The procedure also has a favorable side effect profile, with minimal anterior chamber inflammation, rare IOP spikes, and no formation of peripheral anterior synechiae. In addition, the diode laser has the distinct advantage of being comparatively inexpensive, portable, and multifunctional. Taken together, these benefits make MDLT an attractive option for office-based glaucoma laser surgery.

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The titanium sapphire laser opens a new frontier.

By George R. Reiss, MD

Wortham and Wickham first reported on argon laser trabeculoplasty (ALT) as a potential treatment modality for primary open-angle glaucoma (POAG) in 1973.[1] It was not until Wise and Witter modified the technique, however, that its use became widespread.[2] ALT was thought to increase aqueous outflow by its thermal effect on tissues of the trabecular meshwork (TM). In addition to this "mechanical" theory, researchers demonstrated a biological effect. For example, Van Buskirk reported differences in glycosaminoglycan turnover, cellular density, and cellular biosynthesis.[3]

In time, ophthalmologists began to recognize that ALT produces structural changes, including histopathologically confirmed thermal damage to TM tissue as well as the formation of peripheral anterior synechiae in the angle that are evident on gonioscopy. As a result, the search began for less damaging laser sources. One of the alternatives developed is selective laser trabeculoplasty (SLT), which targets only pigmented TM cells. This modality has become a popular option for laser therapy, because it produces less collateral damage than ALT while achieving a similar rate of success.[4,5]

Attempts to repeat treatment with ALT have unfortunately led to unpredictable results, most likely owing to the structural damage caused by this laser source.[6,7] Because of the limited success, both in pressure drop as well as duration of effect, surgeons have largely ceased re-treating eyes with ALT. As a result of the reduced structural damage demonstrated and possibility of successful retreatment, SLT has become the preferred treatment in many settings. A continued search for even less damaging laser sources has recently led researchers to study the use of a titanium:sapphire laser for trabeculoplasty.

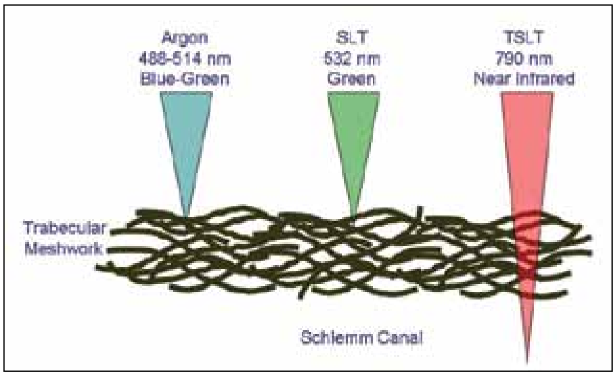
TITANIUM:SAPPHIRE LASER TRABECULOPLASTY

SLT and titanium:sapphire laser trabeculoplasty (TSLT) differ in several ways. Whereas the former uses a frequency-doubled Q-Switched Nd:YAG laser source, TSLT uses a titanium:sapphire laser (Solx 790 Laser; Solx, Inc.). They operate at different wavelengths—790 nm versus the green wavelength of 532 nm, respectively (Table). By delivering more energy per pulse than SLT (80 mJ vs 2 mJ), TSLT penetrates the angle more deeply (Figure 1). This degree of pen-

TABLE. TECHNICAL COMPARISON OF SLT AND TSLT

	SLT	TSLT
Type of laser[a]	Frequency-doubled Q-switched Nd:YAG	Titanium:sapphire
Wavelength	532 nm (green)	790 nm (infrared)
Energy per pulse	0.1-2 mJ	30-80 mJ
Pulse duration	3 ns	7 µs
Pulse rate	Single shot	Single shot and 1 Hz
Spot size	400 µm	200 µm
Peak power (maximum)	666 kW	11 kW

Abbreviations: SLT, selective laser trabeculoplasty; TSLT, titanium:sapphire laser trabeculoplasty.
[a]Using the Selecta II Glaucoma Laser System (Lumenis Inc.) for SLT and the Solx 790 (Solx, Inc.) for TSLT.



(Courtesy of Solx, Inc. Work performed by Jean-Marie Parel, PhD; Francisco Fantes, MD; and Gabriel Simon, MD.)

Figure 1. Comparison of lasers' penetration.

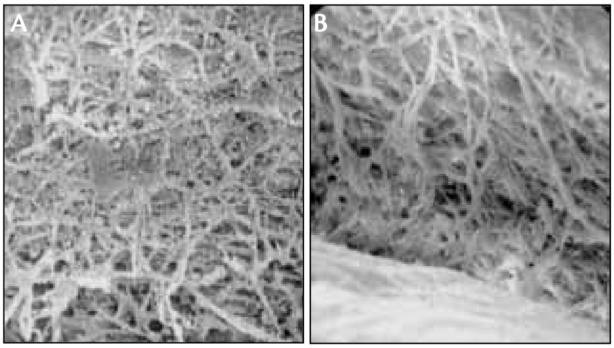


Figure 2. Powdery material that is consistent with pigment (A). TSLT appears to have removed pigment and enlarged trabecular spaces (B). Reproduced with permission of Solx Inc. and Gabriel Simon, MD, PhD, from Simon G, Vivar A, Lowery JA. Clinical results following gonioscopic laser trabecular ablation [GLTA] with a ti:sapphire laser for the treatment of glaucoma. *IOVS*. 35:S838.

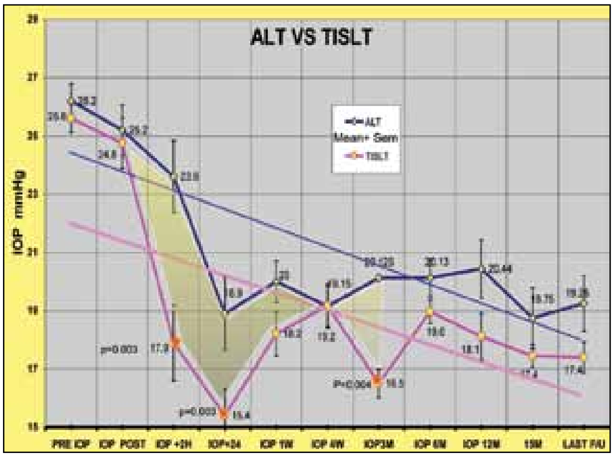


Figure 3. The results of ALT- versus TSLT-treated patients over 18 months. Reproduced with permission of Solx Inc. and Dr. Goldenfeld from Goldenfeld et al.[9]

etration and selective absorption by the pigmented phagocytic cells may explain the minimal damage to the TM.[8] In this respect, TSLT appears to be more like SLT than ALT.

CLINICAL EXPERIENCE

A few studies to date have assessed the efficacy of TSLT. In a controlled study of 40 patients with POAG, 20 subjects were randomized to treatment with ALT and 20 to TSLT (Figure 2).[9] IOPs were recorded at 1 hour, 2 hours, and 1, 3, 6, 12, and 18 months. The investigators found that the mean IOP decreased 8.3 ±2.7 mm Hg in the TSLT group and 6.5 ±4.3 mm Hg in the ALT group. This represented a 32% reduction in the TSLT group compared to 25% in the ALT group. The number of medications decreased from 1.4 ±1.0 to 1.3 ±1.0 in the TSLT group and from 2.1 ±0.8 to 2.0 ±0.8 in the ALT group. IOP spikes occurred in one of the patients who received TSLT and three of the patients who underwent ALT. No major complications, however, were reported in either group. No peripheral anterior synechiae formation was noted in the TSLT eyes, but it was not an uncommon occurrence in the ALT eyes.

A larger study by Shoham et al compared TSLT with ALT in 175 patients. Eighty-five patients received TSLT, and 89 patients underwent ALT for POAG. The results largely confirm those of the previously mentioned research[9] (I. I. K. Ahmed, MD, unpublished data, 2012).

CONCLUSION

TSLT seems to offer many of the advantages over ALT that SLT does, but it may provide additional benefits such as deeper penetration of TM tissue. Future studies should improve ophthalmologists' understanding of TSLT's utility as a treatment for POAG. In particular, a randomized study comparing TSLT with SLT would provide valuable information. ■

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