The Future of Noninvasive Surgeries to Enhance Aqueous Outflow

Sonic energy and the modified delivery of laser energy appear to be the next wave.

BY JEFFREY A. KAMMER, MD

To date, all of the noninvasive procedures that increase aqueous outflow involve the use of a laser to mediate the desired effects. Although these treatment modalities are relatively effective, they all have several limitations. For one, laser trabeculoplasty (LTP) requires a slit lamp for viewing the angle and for the application of laser energy. Another drawback is that these systems are designed such that the patient must sit upright at a slit lamp with his or her head carefully positioned in the headrest. This positioning can sometimes be challenging, particularly for patients with debilitating neck and back pathology. Finally, successful LTP requires that the surgeon have an excellent view of the trabecular meshwork (TM), yet visualization is sometimes limited by the iris configuration, corneal opacities, or patients' lack of cooperation.

The aforementioned obstacles have motivated innovators to seek therapeutic alternatives that will maintain the safety and efficacy of LTP while minimizing its weaknesses. Based on the observation that IOP tends to increase after intra- or extracapsular cataract surgery but typically decreases after phacoemulsification surgery, researchers began investigating sonic energy as a cause of the ocular hypotensive effect. Wang et al reported that a phacoemulsification ultrasound stressor activates the IL-1/NF-κB/ELAM-1 pathway in TM cells.[1] This response initiates a complex and incompletely understood cascade that culminates in an improved outflow facility. The objective finding that sonic energy can mediate IOP lowering has inspired several researchers to pursue this medium and transform it into a clinically meaningful instrument. This article focuses on two procedures: therapeutic ultrasound for glaucoma (TUG) and deep wave trabeculoplasty (DWT). The sidebars by Iqbal Ike Ahmed, MD, FRCSC, and Miho Nozaki, MD, PhD, discuss micropulse laser trabeculoplasty and pattern scanning laser trabeculoplasty, respectively.

(Courtesy of EyeSonix.)

Figure 1. TUG is a portable, stand-alone, lightweight (5-lb) device that can be easily transported to satellite offices.

THERAPEUTIC ULTRASOUND FOR GLAUCOMA

Donald Schwartz, MD, has been an active proponent of transforming sonic energy into an IOP-lowering

MICROPULSE LASER TRABECULOPLASTY

By Iqbal Ike K. Ahmed, MD, FRCSC

The popularity of selective laser trabeculoplasty has risen in recent years owing to its significantly lower laser fluency and enhanced predictability compared to argon laser trabeculoplasty (ALT). Selective laser trabeculoplasty (SLT) has also been found to be equal in efficacy to topical prostaglandin monotherapy at lowering IOP.[1] One of the advantages of SLT compared to ALT has been minimal thermal and collateral tissue damage, with the theoretical benefit of repeatability.

SLT still rarely may cause pressure spikes after treatment, however, in addition to mild and transient inflammation and pain. Growing knowledge about heat stress proteins and cellular response emphasizes that lethal damage to cells is not necessary to provide a therapeutic benefit in retinovascular applications,[2,3] and the same is likely true with glaucoma.

Micropulse technology (Iridex) breaks a continuous-wave laser beam into short, repetitive pulses that allow cooling between laser applications, thereby reducing or preventing thermal damage,[4] as is true for SLT. After setting a level for laser power and a spot size, the surgeon controls thermal exposure with the duration and duty cycle. *Duration* refers to the total length of time that laser energy is delivered, including the rest periods, and *duty cycle* denotes the percentage of time that the laser is delivering energy versus resting. For example, for a pulse duration of 2 milliseconds with a duty cycle of 15%, laser energy would be applied for 0.3 milliseconds followed by a 1.7-millisecond rest period. This pattern would be repeated for the indicated duration.

By using short bursts of laser energy, micropulse laser trabeculoplasty (MLT) has been shown to cause no anatomical effects compared to ALT burns on the trabecular meshwork when evaluated by electron microscopy. Essentially, MLT-treated tissue was similar in appearance to control tissue.[4] MLT seems to be a very gentle treatment for glaucoma, and I look forward to more high-quality peer-reviewed research.

MLT lowered IOP in a phase 2 clinical study,[5] and over the past year, my colleagues' and my early results with modified laser settings have been promising. I have been performing the procedure for a year. My current technique is to use a 532-nm wavelength, 1,000 mW of power, a spot size of 300 µm, a total exposure duration of 300 milliseconds, and a duty cycle of 15%. After a 360° treatment, I have seen approximately a 25% decrease in IOP so far in more than 50 patients. Although I do not yet know how long the effect will last, considering the minimal alteration of tissue with treatment, MLT may be repeatable.

Certainly, one distinguishing feature of MLT is evident: the lack of any sign of treatment during or after the procedure. Typically, blanching of pigment or microcavitational bubbles are evident during laser trabeculoplasty (LTP). This is not the case with the extremely low level of micropulsed energy delivered with MLT. Eyes are generally very quiet postoperatively and so far seem to tolerate MLT extremely well. Importantly, my colleagues and I performing this procedure have seen no IOP spikes after treatment thus far, although, again, our experience is limited to a small number of eyes over the course of 1 year.

MLT is a relatively new method of LTP that uses advances in the delivery of laser energy. Although the published data are relatively early, the procedure seems to hold promise as a viable option for treating open-angle glaucoma. Certainly evident is the value of a safe therapy not involving topical medical drops, as has been clear with SLT and ALT. LTP has a role as first-, second-, and third- or fourth-line therapy. MLT may provide a versatile platform for multiple applications, and micropulse laser therapy appears to offer additional safety. This may be particularly important for patients who are at risk of an IOP spike or for whom inflammation could be problematic. I look forward to gaining more experience and seeing more data.

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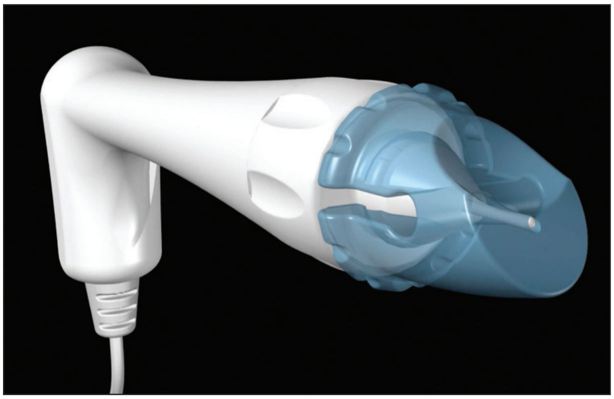
(Courtesy of EyeSonix.)

Figure 2. The tip of the TUG handpiece is placed on the scleral side of the limbus at a 45° angle to the globe. This positioning directs the focal point of the ultrasound energy directly into the TM.



(Courtesy of OcuTherix.)

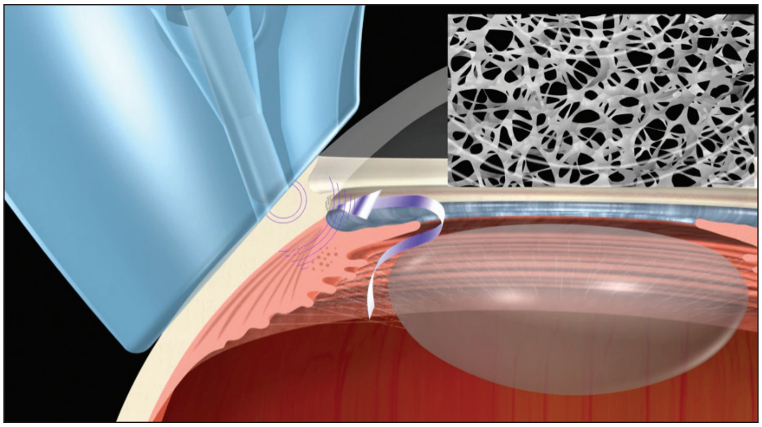
Figure 3. A computer-generated representation of the DWT handpiece.

device. In 2006, he was impressed by the data implicating ultrasound energy as the mediator of a reduction in IOP after phacoemulsification. While reviewing the literature, Dr. Schwartz identified three possible mechanisms through which ultrasound energy could exert its influence: (1) a thermal effect,[2,3] (2) a sonomechanical (vibratory) effect,[4,5] and/or (3) an integrin-induced inflammatory response.[6] Although it is quite possible that the true mechanism is a combination of the three pathways, he focused his attention on the thermal effects of ultrasound.

Dr. Schwartz noted that cytokine release occurred at 42.5°C and that cellular necrosis occurred at 45°C.[7] Given these parameters, he designed an ultrasound unit that created a localized, controlled, limited hyperthermia that produced a sustained temperature of 43°C.

To perform TUG, the physician places an ultrasound probe circumferentially around the limbus at all 12 clock hours (Figures 1 and 2). The tip of the ultrasound probe is positioned on the limbus, 0.5 mm from the cornea, and oriented such that the focal point of the ultrasound is within the TM. The focused ultrasound energy (20,000-100,000 Hz) generates enough heat to reach 43°C without going any higher, thus triggering the cytokine cascade that mediates improved outflow facility.

Although the results of the clinical studies have not been released, Dr. Schwartz provided a glimpse of the data at the 2014 Ophthalmology Innovation Summit.[8] The TUG-3 clinical trial is a prospective study with two groups, both of which were treated with TUG: (1) those who either were naïve to pharmaceutical treatment or had not used any glaucoma medications for 6 months and (2) those who had been actively using glaucoma medications and subsequently underwent a washout. Dr. Schwartz reported that 80% of the treatment-naïve patients experienced a decrease in IOP of 20% or more compared with baseline after 1 year of follow-up. In the group of patients who had previously been treated and completed a washout, 80% had IOPs that were less than or equal to their IOP while on glaucoma drops. Moreover, he stated that the side effect profile of TUG was quite favorable, with no pain and very mild hyperemia.



(Courtesy of OcuTherix.)

Figure 4. DWT uses a specially designed globe-conforming handpiece for focal, mechanical oscillation at the limbus. The low-amplitude and low-frequency sonic energy is transmitted to the TM, where it exerts its effect.

DEEP WAVE TRABECULOPLASTY

Malik Kahook, MD, was also impressed by the intrinsic potential of sonic energy to elicit an IOP reduction. Like Dr. Schwartz, Dr. Kahook was inspired by the observation that IOP often decreases after

PATTERN SCANNING LASER TRABECULOPLASTY

By Miho Nozaki, MD, PhD

Pattern Scanning Laser Trabeculoplasty (PSLT) technology (not available in the United States; Topcon Medical Laser Systems) is a new approach to treating glaucoma via the trabecular meshwork (TM). Pattern scanning laser technology provides a computer-guided treatment method that applies a sequence of patterns onto the TM. Calculated alignment of each pattern ensures that consecutive treatment steps are pieced together around the TM without overlap or excessive gaps.

THE PROCEDURE

The clinician titrates laser power using a single 100-µm spot to achieve light blanching of the TM, with 10-millisecond laser pulses applied to the inferior segment of the eye, where pigmentation is often most densely concentrated. After titration, power is maintained, but the pulse duration is reduced to 5 milliseconds. The pulse energy is thus cut in half, which makes the treatment outcome ophthalmoscopically invisible. Using the inferior segment for titration helps to ensure that the 5-millisecond treatment pulses will be invisible in all segments of the TM.

Physicians can choose to treat half or all of the TM. Treatment is administered in 32 steps for 360º of the TM. The aiming beam automatically rotates. When I treat patients, I rotate the gonio laser contact lens to set the aiming beam on the TM.

After the described steps, treatment is complete.

RESEARCH

PSLT was developed based on a clinical understanding of the nonlethal tissue effects of selective laser trabeculoplasty (SLT), and the clinical outcomes of the two procedures are comparable. Turati and colleagues reported the initial experience with PSLT 532 nm, and the overall IOP reduction rate was 24%, similar to SLT.[1] PSLT causes no damage to the TM. Lee and colleagues compared PSLT to argon laser trabeculoplasty in cats and examined morphologic changes in the TM. The investigators found that PSLT caused less thermal damage to the TM than ALT.[2] Like SLT, PSLT is theoretically repeatable. The procedure also has similar IOP-lowering effects as SLT.[1,3]

My colleagues and I conducted a retrospective chart review of 21 patients (24 eyes) with open-angle glaucoma who received SLT or PSLT with the Pascal Streamline 577 (Topcon Medical Laser Systems). All eyes were treated for 360º. The average follow-up period was 11 ±4 months in the PSLT group and 18 ±9 months in the SLT group ($P = .10$), but there was no statistically significant difference in either group. In the PSLT group, the mean IOP at baseline and 6 months was 21.8 (standard deviation [SD], 5.0) and 14.3 (SD, 3.3) mm Hg, respectively. In the SLT group, the mean IOP at baseline and 6 months was 23.8 (SD, 6.7) and 17.3 (SD, 3.4) mm Hg, respectively. There was no significant difference between PSLT and SLT in terms of the average IOP reduction from baseline (33% and 22%, respectively). We found PSLT to be as effective as SLT at lowering IOP over a 6-month period.[4]

Although further research is needed to verify the extent and the long-term stability of the IOP reduction, PSLT with a 577-nm wavelength appears to be as effective as SLT at lowering IOP over a 6-month period.

Further information on PSLT is available online at tmlsinc.com.

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uncomplicated phacoemulsification-assisted cataract extraction.[9] His clinical interest peaked when it was reported that this drop in IOP was mediated by ultrasonic activation of a stress response within TM cells that culminated in cytokine release and the modification of outflow channels.

Whereas TUG relies on ultrasound energy, Dr. Kahook favors the use of a lower frequency to exert a therapeutic effect. His research resulted in the development of a new procedure that he named *deep wave trabeculoplasty* (Figure 3). This technology is designed to enhance aqueous outflow through the TM without damaging tissue. DWT operates in the sonic range and, when applied over the limbus, generates enough mechanical oscillation to cause focal stretching and relaxation of the TM cells (Figure 4). A resultant stress response within the TM presumably stimu-

(Courtesy of OcuTherix.)

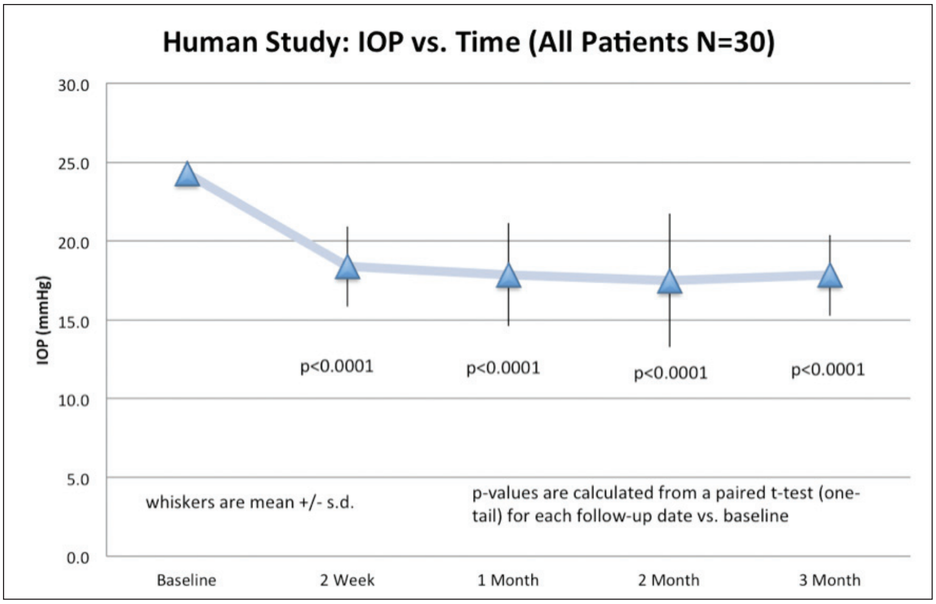

Figure 5. The statistically significant decrease in IOP after DWT treatment in human subjects.

> "Although laser energy has been the dominant medium for noninvasive glaucoma surgery, nascent evidence suggests that sonic energy can provide comparably efficacious IOP lowering."

lates a cytokine cascade that positively influences aqueous outflow.[10]

To date, two human trials have studied the safety and efficacy of DWT. The first recruited a cohort of patients with primary open-angle glaucoma whose IOPs were higher than 23 mm Hg after a washout of their medications. The 30 patients who met the inclusion and exclusion criteria underwent DWT in one eye, while the fellow eye served as the control. The researchers noted a significant (26%) decrease in IOP in the treated group over the 3-month follow-up period (Figure 5). Moreover, they reported that only 30% of the patients in the DWT group required rescue medications to achieve the target IOP, whereas 100% of the controls restarted IOP-lowering medications. No significant side effects were reported. Nor was there any evidence of anterior chamber inflammation in the patients treated with DWT.

The second clinical trial is a prospective, randomized study in which glaucoma patients are assigned to one of three groups: DWT, selective laser trabeculoplasty, or sham treatment. The primary endpoints and other secondary efficacy parameters will be monitored over a 2-year period. This study is currently being completed in the Philippines, and results are expected later this year.

CONCLUSION

Although laser energy has been the dominant medium for noninvasive glaucoma surgery, nascent evidence suggests that sonic energy can provide comparably efficacious IOP lowering. Moreover, this new technology offers the potential advantages of being cost-effective, portable, and ergonomic with fewer potential side effects. The results of the prospective, randomized clinical studies will help define the potential impact that these new treatments will have on future clinical practice. ■

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