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A Comparison of Argon Laser and Diode Laser Photocoagulation of the Trabecular Meshwork to Produce the Glaucoma Monkey Model

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Purpose: To create an experimental glaucoma monkey model using high-power diode laser photocoagulation of the trabecular meshwork, and to compare this with the experimental glaucoma monkey model induced by argon laser photocoagulation of the trabecular meshwork.

Methods: One eye each of eight adult cynomolgus monkeys underwent repeated application of diode laser photocoagulation of the trabecular meshwork until sustained intraocular pressure (IOP) elevation was achieved. 50 to 120 spots were applied to midtrabecular meshwork for 360°; spot size, 75 μm; power, 1.2 W; duration, 0.5 seconds. Intraocular pressure, tonographic outflow facility, and ophthalmoscopically and photographically documented optic nerve head evaluations were carried out before and after treatment. Data were compared retrospectively with similar data from an experimental glaucoma monkey model after argon laser photocoagulation of the trabecular meshwork ($n = 10$).

Results: The average number of laser treatments to achieve stable IOP elevation was 3.0 with both diode and argon laser trabecular treatments ($p > 0.99$). On week 4 after initial pressure elevation, peak IOP was greater—($p < 0.05$) 43.0 mmHg ± 2.4 mmHg (mean ± SEM) and 37.4 mmHg ± 1.3 mmHg—in the diode laser-induced than in the argon laser-induced glaucomatous eyes, respectively. Outflow facility (μl/min/mmHg) was reduced ($p < 0.001$) in both diode (0.09 ± 0.01 μl/min/mmHg) and argon (0.10 ± 0.01 μl/min/mmHg) laser-induced glaucomatous eyes compared with untreated fellow eyes. Both the diode and argon laser techniques produced the earliest signs of optic nerve head excavation within about one month of IOP elevation.

Conclusions: Repeat diode laser photocoagulation of the trabecular meshwork produced higher ($p < 0.05$) IOP elevation than argon laser photocoagulation of the trabecular meshwork in this study. No significant differences in outflow facility and optic nerve head change were observed between these two laser techniques. The experimental glaucoma monkey model can be created with either the diode or argon laser photocoagulation of the trabecular meshwork.

Key Words: Diode laser photocoagulation—Argon laser photocoagulation—Experimental glaucoma monkey model—Intraocular pressure—Outflow facility—Optic nerve head cupping.

The monkey eye is very similar to the human eye and the glaucoma produced by repeated intense argon laser photocoagulation of the trabecular meshwork (ALPT) mimics human open-angle glaucoma (1). A sustained, moderate intraocular pressure (IOP) elevation is produced that leads to decreased outflow facility (C) and cupping of the optic nerve head (ONH). This model of

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glaucoma has provided information about physiology and pathology of glaucoma (2–4), and has been used to evaluate new therapeutic agents and surgical techniques for the management of glaucoma (5–10).

Clinical studies have demonstrated that the diode laser can be used to perform diode laser trabeculoplasty and produces results comparable to these obtained with the argon laser (11,12). Thus, this study was performed to determine if intense application of the diode laser photocoagulation of the trabecular meshwork (DLPT) could be used to create the experimental glaucoma monkey model (EGMM). We also were interested in learning whether the EGGM would differ in any important respects from that created by the argon laser. A retrospective analysis was performed comparing the diode laser with the argon laser in creating the EGMM and on the resultant IOP, C, and ONH cupping.

MATERIALS AND METHODS

Eight adult cynomolgus monkeys (7 female, 1 male), each weighing 3 kg to 5 kg, were used in the study. The monkey eyes were healthy with no previous history of surgical, laser, or experimental drug treatment. The animals were anesthetized with 3 mg/kg to 5 mg/kg of ketamine hydrochloride intramuscularly and one drop of 0.5% proparacaine hydrochloride was topically applied 5 minutes before laser treatment and before all measurements. Ten additional cynomolgus monkeys previously treated with the argon laser formed the historical comparison group.

A portable semiconductor diode laser (IRIS Medical Instruments Inc., Mountain View, CA, U.S.A.), emitting at wavelength of 810 nm and which could be attached to a standard slit-lamp microscope, was used in the study. The maximum available power was 1.2 W. The aiming beam was provided by a low-power, red-emitting laser diode. One eye each of 8 monkeys underwent repeated diode laser photocoagulation to the midtrabecular meshwork for 360°, using a single-mirror Goldmann goniolens (Ocular Instruments Inc., Bellevue, WA, U.S.A.) specially designed for monkeys. Laser settings for each treatment session were as follows: DLPT, 50 to 120 spots; spot size, 75μm; power, 1.1 W to 1.2 W; duration, 0.5 seconds; ALPT, 65 to 120 spots; spot size, 50μm; power, 1.1 W to 1.5 W; duration, 0.5 seconds. The duration of 0.5 seconds for diode laser treatment was chosen so as to be identical to that used for argon laser treatments; other parameters were chosen by initial experimentation to achieve initial IOP elevations. The sessions were repeated two or three weeks apart until sustained IOP elevation was achieved. All monkeys were observed from 1 to 12 months after the last laser treatment.

Diurnal IOP was measured hourly for six hours beginning at 9:30 AM with a calibrated pneumatonometer (Mentor, Model 30 Classic™, Norwell, MA, U.S.A.) before laser treatment and weekly after laser treatment. Outflow facility was measured using an electronic indentation tonographer (Alcon EDT-103, Fort Worth, TX, U.S.A.) before laser treatment and on week 4 after the last laser treatment. Optic nerve head evaluation was performed by indirect ophthalmoscopy before laser treatment and weekly after laser treatment for one month, and once a month thereafter. Stereoscopic disc photographs were taken at the same time as indirect ophthalmoscopic examinations. Slit-lamp examination was performed before laser treatment and weekly after laser treatment for one month. Gonioscopic examination was carried out before laser treatment and once a month after laser treatment for three months.

Data were compared with a historical control of 10 cynomolgus monkeys treated unilaterally by ALPT. The two-tailed unpaired *t* test was used for statistical analyses of the number of laser treatments performed, IOP, and C in EGMM as created by DLPT versus ALPT. Comparisons between treated and fellow untreated control eyes were made using the two-tailed paired *t* test. The Fisher exact test was used for comparison of gradings of anterior-chamber inflammatory reactions between DLPT and ALPT. All experimental studies complied with the Association for Research in Vision and Ophthalmology Resolution on the Use of Animals in Research and were approved by the Mt. Sinai School of Medicine Animal Care and Utilization Committee.

RESULTS

Prior to laser treatment, the anterior segment and optic disc appearance of all animals were unremarkable. The peak diurnal IOP was 19.9 mmHg ± 0.6 mmHg (mean ± SEM) (DLPT) versus 18.5 mmHg ± 0.5 mmHg (ALPT), C was 0.64 μl/min/mmHg ± 0.03 μl/min/mmHg (DLPT) versus 0.70 μl/min/mmHg ± 0.03 μl/min/mmHg (ALPT), and cup/disk (C/D) ratios were 0.30 ± 0.04 (DLPT) versus 0.26 ± 0.03 (ALPT). There were no significant differences ($p > 0.05$) of baseline IOP, C, and C/D between the DLPT and ALPT groups (Table 1).

More than one laser treatment was required to produce a permanent rise of IOP in all eyes treated with either DLPT or ALPT. The average number of laser treatments to achieve the sustained IOP elevation was 3.0 ± 0.3 (DLPT) versus 3.0 ± 0.3 (ALPT) ($p > 0.99$). During

TABLE 1. *The baseline intraocular pressure, outflow facility, and cup/disc ratio before diode or argon laser photocoagulation of the trabecular meshwork*

	Peak diurnal IOP Mean mmHg ± SEM	C Mean µl/min/mmHg ± SEM	C/D Mean ± SEM
DLPT (n = 8)	19.9 ± 0.6	0.64 ± 0.03	0.30 ± 0.04
ALPT (n = 10)	18.5 ± 0.5	0.70 ± 0.03	0.26 ± 0.03

ALPT, argon laser photocoagulation; C, outflow facility; C/D, cup/disc ratio; DLPT, diode laser photocoagulation; IOP, intraocular pressure; SEM, standard error of mean.

DLPT treatment, a mild blanching of the trabecular meshwork was frequently observed, presumably due to heavy pigmentation of the trabecular meshwork of monkey eyes. Compared to ALPT, however, the tissue reaction was less and gas bubble formation was not observed at the settings used to create DLPT. Gas bubbles were observed with more than 50% of burns with ALPT.

An IOP spike occurred after all laser treatments with either the argon or the diode laser. For example, at four hours after the final laser treatment, IOP was 45.1 mmHg ± 2.0 mmHg (DLPT) and 38.3 mmHg ± 2.1 mmHg (ALPT). This difference was significant ($p < 0.05$), but this early pressure elevation probably was due to transient obstructioon of outflow pathways by debris associated with an intense inflammatory reaction. We therefore did not consider it further.

The first day after DLPT or ALPT treatments, acute iritis was noted in all monkey eyes with one to two plus (scale of 0 to 4) anterior chamber flare and cells. During the first week after laser treatment, 5 of 8 (63%) DLPT-treated eyes had pigmentary keratic precipitates on the endothelial surface of the cornea versus 4 of 10 (40%) ALPT-treated eyes ($p > 0.60$). Posterior synechiae developed in 7 of 8 (88%) DLPT-treated eyes compared to 5 of 10 (50%) ALPT-treated eyes ($p > 0.20$). A fibrinous anterior chamber reaction was seen in 4 of 8 (50%) DLPT-treated eyes, while this was not observed in any of the ALPT-treated eyes ($p < 0.05$). The anterior chamber reactions resolved within three to four weeks after either DLPT or ALPT treatments. Gonioscopic examination revealed that all eyes after DLPT or ALPT had an open angle with indistinct angle structures, irregular pigmentation of the trabecular meshwork, and scattered peripheral anterior synechias to scleral spur or cornea. Peripheral anterior synechias to the cornea was noted in 1 of 8 DLPT-treated eyes, but in none of the ALPT-treated eyes. Slit-lamp examination demonstrated rubeosis iridis in 1 of 8 DLPT-treated eyes, and in 2 of 10 ALPT-treated eyes.

The IOP frequently fell after initial laser treatment for about one week; this occurred in 50% of eyes treated with either DLPT or ALPT. If the IOP subsequently rose, it generally occurred one to two weeks after treatment. On week 4 after initial pressure elevation, the peak IOP was greater ($p < 0.05$) in the DLPT-treated eyes, 43.0 mmHg ± 2.4 mmHg, than in the ALPT-treated eyes, 37.4 mmHg ± 1.3 mmHg (Table 2). The average range of diurnal fluctuation in IOP was 9.8 mmHg ± 1.4 mmHg (DLPT) versus 9.8 mmHg ± 0.8 mmHg (ALPT) ($p > 0.90$). By eight weeks after final laser treatment, peak IOP was still higher ($p < 0.05$) in the DLPT-treated eyes (42.6 ± 3.0 mmHg) than in the ALPT-treated eyes (33.7 ± 1.7 mmHg).

At four weeks after final treatment, C was decreased by both DLPT (0.09 ± 0.01 µl/min/mmHg in glaucomatous eyes vs. 0.62 ± 0.03 µl/min/mmHg in untreated fellow eyes, $p < 0.001$), and ALPT (0.10 ± 0.01 µl/min/mmHg in glaucomatous eyes vs. 0.70 ± 0.03 µl/min/mmHg in fellow eyes, $p < 0.001$). Outflow facility did not differ ($p > 0.30$) between DLPT-treated and ALPT-treated eyes (Table 3).

Both DLPT and ALPT produced the earliest signs of ONH excavation within one month of IOP elevation. These signs included posterior bowing of the ONH and the peripapillary region, which was noted in 6 of 8 (75%) DLPT-treated eyes and 6 of 10 (60%) ALPT-treated eyes ($p > 0.80$) at the one-month examination. An initial conical shallow cupping with minimal increase in C/D ratio was observed in all 8 eyes treated with DLPT and all 10 eyes treated with ALPT. After the initial phase of cupping, a gradual increase in C/D ratio of the ONH was observed after persistent IOP elevation, resulting in a deeper cup with steeper walls, an increase in the area of pallor, a localized thinning of the disc rim tissue, and nerve fiber layer defects. If the IOP elevation remained extremely high for a considerable time, total cupping with undermining of the rim ultimately occurred in both DLPT- and ALPT-treated eyes.

TABLE 2. *Peak intraocular pressure after repeat diode or argon laser photocoagulation of the trabecular meshwork*

	Peak intraocular pressure Mean mmHg ± SEM		
	Week 1	Week 2	Week 4
DLPT (n = 8)	24.2 ± 2.1	33.1 ± 3.1	43.0 ± 2.4*
ALPT (n = 10)	26.9 ± 2.1	31.8 ± 1.6	37.4 ± 1.3

ALPT, argon laser photocoagulation; DLPT, diode laser photocoagulation.

* Significant difference in intraocular pressure between DLPT- and ALPT-treated eyes (two-tailed unpaired *t* test, $p < 0.05$).

TABLE 3. *Outflow facility at week 4 after repeat diode or argon laser photocoagulation of the trabecular meshwork*

	Outflow facility Mean μl/min/mmHg ± SEM	
	Treated eyes	Fellow eyes
DLPT (n = 8)	0.09 ± 0.01*	0.62 ± 0.03
ALPT (n = 10)	0.10 ± 0.01*	0.70 ± 0.03

ALPT, argon laser photocoagulation; DLPT, diode laser photocoagulation.

* Significant difference in outflow facility between DLPT- or ALPT-treated eyes and untreated fellow eyes (two-tailed paired *t* test, $p < 0.001$).

DISCUSSION

Our study showed that both DLPT and ALPT produced sustained elevations of IOP. There was no difference between the average number of laser treatments necessary to obtain stable IOP elevation using these two laser techniques. However, DLPT produced higher ($p < 0.05$) IOP elevation than ALPT. The main differences between the techniques of DLPT and ALPT were the power setting and the spot size used. The mean power setting was 1.2 W (DLPT) versus 1.4 W (ALPT), and the spot size was 75 μm (DLPT) versus 50 μm (ALPT). The energy density of DLPT was therefore less than ALPT, but it nevertheless caused higher elevations of IOP.

This may be related to the different photocoagulative effects of the two wavelengths (diode: 810 nm, argon: 488.0–514.5 nm) on the treatment site. A complex biologic response to irradiation with an increase in trabecular cell division may play an active role in the effect of a laser on the aqueous outflow tissue (13). Histologic study of the effect of photocoagulation on the trabecular meshwork of the human eye in vitro shows that the diode laser causes deeper lesions than the argon laser, although the appearance of diode and argon burns are similar (14). Possibly this results in more damage to the trabecular meshwork, leading to more obstruction to aqueous outflow with DLPT than with ALPT. It may be that deeper lesions are more injurious to the blood–aqueous barrier, explaining the greater anterior chamber inflammation seen after diode treatment.

Outflow facility was markedly reduced in all DLPT- and ALPT-treated eyes. Mean C did not differ between the DLPT and ALPT groups. Several peripheral anterior synechias were present in all eyes after DLPT and ALPT treatments, but the anterior chamber angle remained grade 3–4 open. Histopathologic studies have demonstrated an obstruction of the outflow channels by cellular materials and tissue debris and a fibrin-like "pseudomembrane" overlying the trabecular spaces in the early days after laser treatment (15–17). Three to four weeks after laser treatment, there is much less cellular material and debris present, and a proliferation of endothelial cells and trabecular scarring with obliteration of Schlemm canal are observed (17). An increase in resistance to aqueous outflow is the result.

A common observation after laser photocoagulation of the trabecular meshwork has been acute anterior uveitis. Clinical studies have demonstrated that DLPT-treated eyes have a lesser (18) or similar (11,12) degree of anterior chamber inflammation than ALPT-treated eyes. In our monkey study, however, DLPT-treated eyes had more marked iridocylitis than ALPT-treated eyes. A collection of fibrin with cells in the anterior chamber occurred in 50% of DLPT-treated eye, but did not occur in any of the ALPT-treated eyes ($p < 0.05$). The differences in these two treatment groups did not reach statistical significance in all the signs of anteriror chamber inflammations probably because of the small sample size. After the acute inflammatory reaction subsided, more peripheral anterior synechias and posterior synechiae developed in DLPT eyes than ALPT eyes, which might explain the higher IOP in DLPT eyes.

High-powered DLPT or ALPT induced a sustained, moderate to high IOP elevation that caused optic nerve damage. The development and progression of optic disc cupping occurred in both DLPT and ALPT eyes. There were no significant differences in the early signs of cupping or morphologic characteristics of progressive cupping comparing these two laser techniques. In the early phases of cupping, most laser-induced glaucomatous monkey eyes demonstrated posterior bowing of the ONH and peripapillary tissues. The posterior displacement was of sufficient magnitude to produce a characteristic shadow around the optic disc. Possibly the thin sclera of monkey eyes might have allowed the entire region to stretch posteriorly, a characteristic also observed in younger human patients with glaucoma (15).

CONCLUSION

The EGMM can be induced by both DLPT and ALPT using the settings reported here. The magnitude of IOP elevation with DLPT appears to be greater than with ALPT in this study. No significant differences in outflow facility or ONH changes are observed comparing these two laser techniques. We have thus shown that there are many similarities but some differences between the type of EGMM that results from argon versus diode laser treatment with the parameters we have chosen. For certain purposes the higher IOP achieved by DLPT may be preferable, while for others, this might be a disadvantage.

It may be that with other parameters DLPT could be used to achieve lower final IOP than that which was seen here. Additional studies will be required to explore this possibility.

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